The Department of Homeland Security's

National Infrastructure Simulation & Analysis Center

Farmers in Indonesia burn dead chickens, although the government in Jakarta said it would vaccinate – not cull – infected birds
BBC News Photo

Joint NISAC - CIP/DSS

Analysis of Avian Influenza Virus Issues for the Catastrophic Assessment Task Force (CATF) Table-Top Exercise

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Executive Summary

This document summarizes analyses of the factors affecting a potential outbreak of avian influenza on the United States. Produced by NISAC (a DHS/IP program, a core partnership of Sandia and Los Alamos National Laboratories) and CIP/DSS (a DHS/S&T program, a core partnership of Sandia, Los Alamos, and Argonne National Laboratories), the document provides results for epidemiological, economic, and infrastructure studies, with the intent of aiding decision makers by analyzing the consequences and tradeoffs associated with decisions at different points in the course of a pandemic. DHS's information needs are both short-term and long-term, and while containing and mitigating the consequences of an outbreak is of central concern, the continued functioning of infrastructures must also be addressed to ensure social services and overall quality of life. Optimal decision-making will depend greatly on the specifics of any potential pandemic. A policy decision that may be optimal for the initial stages of disease outbreak could be deleterious several weeks or months later.

The analysis results were developed specifically to support an upcoming table-top exercise. Models are based on specific assumptions and therefore show the relative efficacies of different mitigation measures. There are uncertainties associated with any absolute numerical results. Once more is known about a disease outbreak and parameters, the simulations can be run with more accurate assumptions.

Our epidemiological analysis results are summarized as follows:

Effectiveness of combating the initial epidemic in Southeast Asia:

- For the unmitigated case (no travel restraints in either the US or Thailand), the epidemic reaches its peak in the US 29 weeks after the 1st case appears in Thailand. If the initial epidemic is reduced by factor of 200, then the peak in the US would be delayed by three weeks. Even so, the pandemic runs its course and there are no reductions in the number of deaths and infected in the US, with the exception of consequence mitigation actions that benefit from the three week delay.

Controls on international and inter-region US travel:

- Since non-symptomatic infected travelers will account for 70% of the infectious source from international travelers, a policy of quarantining

symptomatic international arriving travelers could at best reduce the infectious source by 30%. Such a policy would delay the US epidemic by about 5 days.

- In addition to preventing entry of all symptomatic persons, reducing the total number of travelers originating in regions in early epidemic stage could provide a month or two of delay in the US epidemic if travel can be restricted by a factor of ten or fifty from infected regions during the early growth stage of their epidemic.
- Reducing the number of infected people arriving at a city or region from somewhere else in the US from twenty per day to five per day delays the onset of an epidemic by close to three weeks. Curtailing the infected travelers from five per day to one will give an additional 3 week delay.

Optimal administration of vaccines:

- If the vaccine supply is limited or non-existent, a "children and teenagers first" vaccination strategy could be effective in thwarting an influenza epidemic. All others within the community would be protected by herd immunity rather than direct vaccination. Substantial reductions in infection and death rates could be achieved if the vaccine is administered to and effective for ~60% of the children and teenagers (~17% of the general population).
- Vaccination at lower than optimal levels or use of partially effective vaccines will reduce the total number of illnesses and their peak while prolonging the total period of the epidemic. Whatever vaccine is available at the time should be used as rapidly as possible, regardless of its effectiveness.

Antiviral usage strategies:

- Delay in intervention will dramatically increase the total number of cases and deaths.
- For a homogeneous population with a reproductive (or infectivity) number, R_0, of 1.8, a timely mass antiviral treatment of 55% of the simulated population slows influenza transmission, and can halt an epidemic when above 60% of the population is provided antivirals.
- If antivirals are provided only to contacts (previous, current, and future) of infected individuals, then the success of the contact tracing policy depends upon accurate identification of possible infective contacts, and the speed with which antivirals can be distributed.
- For reproductive (or infectivity) numbers (R_0) less than 2.0, targeted administration of antiviral drugs helps to control the spread until vaccine is developed, produced, distributed, and has had time to produce an immune response. For a heterogeneous population composed of children/teenagers with higher R_0 and adults with lower R_0, targeting of the children/teenagers with antivirals can be effective.
- Timely ring delivery of limited antivirals can reduce the number of cases and shorten the epidemic drastically.

Design of structured social distancing:

- In the absence of effective vaccines and antivirals, social distancing of "children and teenagers only," could be highly effective. A social distancing policy would require those under 18 years of age to be restricted primarily to their homes for the duration of the epidemic while adults continue to work and interact within the community as normal. If implemented and with full compliance, reductions in the number of people who are infected or die are very high. If compliance is relaxed so that children and teenagers maintain some portion of their normal social contacts outside the family, the number of people that are infected or die may still be greatly reduced.

Combining strategies at a National Level:

- For very aggressive viruses, a sophisticated combination of therapeutic and social distancing measures (including the wearing of masks, quarantine, school closure, and/or travel restrictions) may be necessary to control the spread of the pandemic.

National and Regional Economic Analyses Indicate:

- The scenario could lead to an estimated $600 billion loss in GDP (6%) in the year of the pandemic and a loss of almost nine million jobs. Supply shocks, driven by lack of available workers, slightly outweigh other factors reducing the GDP by $350 billion. Demand shocks are also quite significant, causing the loss of about $230 billion in GDP (2.4%) and a loss of approximately 4 million jobs.

- The population shock (the loss of life) contributes $28 billion to this loss of output in the first year and grows steadily to $37 billion after 10 years. In discounted present value terms, the reduction is $274 billion to the GDP over a 10-year horizon. This is a permanent structural change to the economy causing the population and economy to be on a different growth trajectory than before the outbreak.

- Industries with significant face-to-face transactions (mass-transportation, restaurants, tourism) will see a sharp initial decrease in overall demand. Through the course of the first year, industries suffering the largest output declines include: arts and entertainment, mining, government services, finance and insurance, retail trade and forestry. The total loss of output is a function of the total number of workers lost to morbidity and mortality and the extent to which the industry depends on labor.

NISAC Contacts:
Jon MacLaren
DHS-IP
(202) 282-8719;
e-mail: jon.m.maclaren@dhs.gov

Theresa Brown
Sandia National Laboratories
(505) 844-5247;
email: tjbrown@sandia.gov

Randy E. Michelsen
Los Alamos National Laboratory
(505) 665-1522;
email: rem@lanl.gov

CIP/DSS Contacts:

DHS S&T Program Manager

Sharon DeLand
Sandia National Laboratories
(505) 844-8740
email: smdelan@sandia.gov

Dennis Powell
Los Alamos National Laboratory
(505) 665-3839
Email: drpowell@lanl.gov

Michael Samsa
Argonne National Laboratory
(630) 252-4961
msamsa@anl.gov

NISAC contributors (LANL):	Phillip D. Stroud, Sara Y. Del Valle, Sid J. Sydoriak, James P. Smith, Susan M. Mniszewski, Jane M. Riese, Timothy C. Germann
CIP/DSS contributors (LANL):	Jeanne M. Fair, Dennis R. Powell, Rene J. LeClaire
CIP/DSS contributors (SNL):	Nancy S. Brodsky, Mark A. Ehlen, Verne W. Loose, Robert J. Glass, Jason H. Min, Theresa J. Brown, Paul G. Kaplan, Lory Cooperstock, Vanessa N. Vargas, Kevin L. Stamber

TABLE OF CONTENTS

Analysis of Avian Influenza Virus Issues for the Catastrophic Assessment Task Force (CATF) Table-Top Exercise

1 Introduction

NISAC and CIP/DSS prepared this document to support a Principals-level table-top exercise that will address policy issues surrounding a potential global avian influenza (AI) pandemic. Our intent is to provide information to aid in decision-making by analyzing the consequences and tradeoffs associated with decisions at different points in the course of a pandemic. The timeline by which a potential pandemic might unfold is unknown, but it will depend upon disease parameters, policies, and actions that are also as yet unknown. We hope that this document sheds light not only on the potential consequences and tradeoffs associated with decisions, but on the complex set of interacting systems that will determine the course of the potential outbreak.

Over the past several years, NISAC and CIP/DSS have developed a suite of models to analyze the spread of infectious diseases. Individual models rely on different methods and assumptions, but in combination they form a suite of tools useful for looking at different aspects of disease development, spread, and mitigation. The model results show the relative efficacies of different mitigation measures and are presented in detail in Section 4. Relevant results and insights gained from these analyses are brought forward into Section 2.1, and applied to the policy issues relevant to the table-top exercise in Section 3.

With regard to modeling and mitigation measures, it is important to note that:

- Models are based on artificial communities and therefore show the relative efficacies of different mitigation measures. There are uncertainties associated with any absolute numerical results. Once more is known about a disease outbreak and parameters, the simulations can be run with more accurate assumptions.
- Most mitigation measures slow the disease spread, providing time for the production of an effective vaccine. Development of resistance or immunity, either by contracting influenza or by vaccination, remains the primary mechanism for slowing and eventually halting an influenza pandemic once it has begun.

- Use of antiviral drugs can lessen the severity of the illness, and permit the development of antibodies for resistance and immunity. However, over the long-term, viruses have been known to mutate into more drug-resistant forms.

2 Overview of Important Issues

2.1 Critical Issues, Insights, and Unexpected System Failure Points

A brief summary of the model results is given in Section 4.1. The following points have been distilled from that summary:

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- Industries with significant face-to-face transactions (mass-transportation, restaurants, tourism) will see a sharp initial decrease in overall demand. Through the course of the first year, industries suffering the largest output declines include: arts and entertainment, mining, government services, finance and insurance, retail trade and forestry. The total loss of output is a function of the total number of workers lost to morbidity and mortality and the extent to which the industry depends on labor.

Additional concerns include:

- Antivirals: In order to be effective, antivirals must be administered within a day of an infected person becoming symptomatic (note: WHO advises within 48 hours of becoming ill, but the effectiveness drops very quickly once symptoms begin). This means the distribution of antivirals must take place *before* symptoms occur and individuals must use them only *after* they have been exposed to the pandemic strain but must initiate the course *within* 24 hours of symptom emergence for effective treatment. While avoiding panic, potentially exposed populations must seriously evaluate every possibly symptomatic day. This sort of regimen is very difficult to manage, particularly over long periods of time.

- There will be high costs associated with the pandemic, much of which will not be covered by insurance. An indirect cost of not treating the uninsured infected population will be further spread of the disease.

- It should be expected that individuals entering this country without documentation (crossing the border where there are no quarantine stations) may be conduits for the introduction of the disease.

- If we make a vaccine from the outbreak strain, then suppress the outbreak, we will not know the efficacy of this vaccine against a mutated or new strain.

- The overwhelming demand that will be put on the healthcare system may need further investigation. Insufficient hospital beds – in winter hospitals are already at 110%, plus workers won't be coming in.

- If the US provides a large supply of vaccines and antivirals to Southeast Asia in an effort to contain an outbreak, there may be pressure from within the US to provide these supplies in such a manner as to test the efficacy of the drugs and treatment strategies, despite the preference for a particular strategy as dictated by the current state of research. While it might be technically advantageous to the rest of the world to have a research component included in our first response, significant medical ethics questions could arise due to the element of human experimentation. The US Government should be prepared to address this issue.

2.2 Decision Trees

It is helpful to look at the unfolding of this scenario in terms of decision and event trees which provide logical structures for the analyses and decisions that will be required. The decision tree below is an illustration of treatment options, a single component of the scenario. This simplified view illustrates how our response will depend upon both the disease parameters and the efficacy of our treatments, and that there are currently uncertainties inherent in both. Given the conditions within the scenario (a highly contagious disease with high mortality, the potential to be widespread, without sufficient vaccines or prophylaxis for mass distribution) the decision space that needs to be evaluated is targeted vaccination, targeted prophylaxis, quarantine and treatment of symptoms.
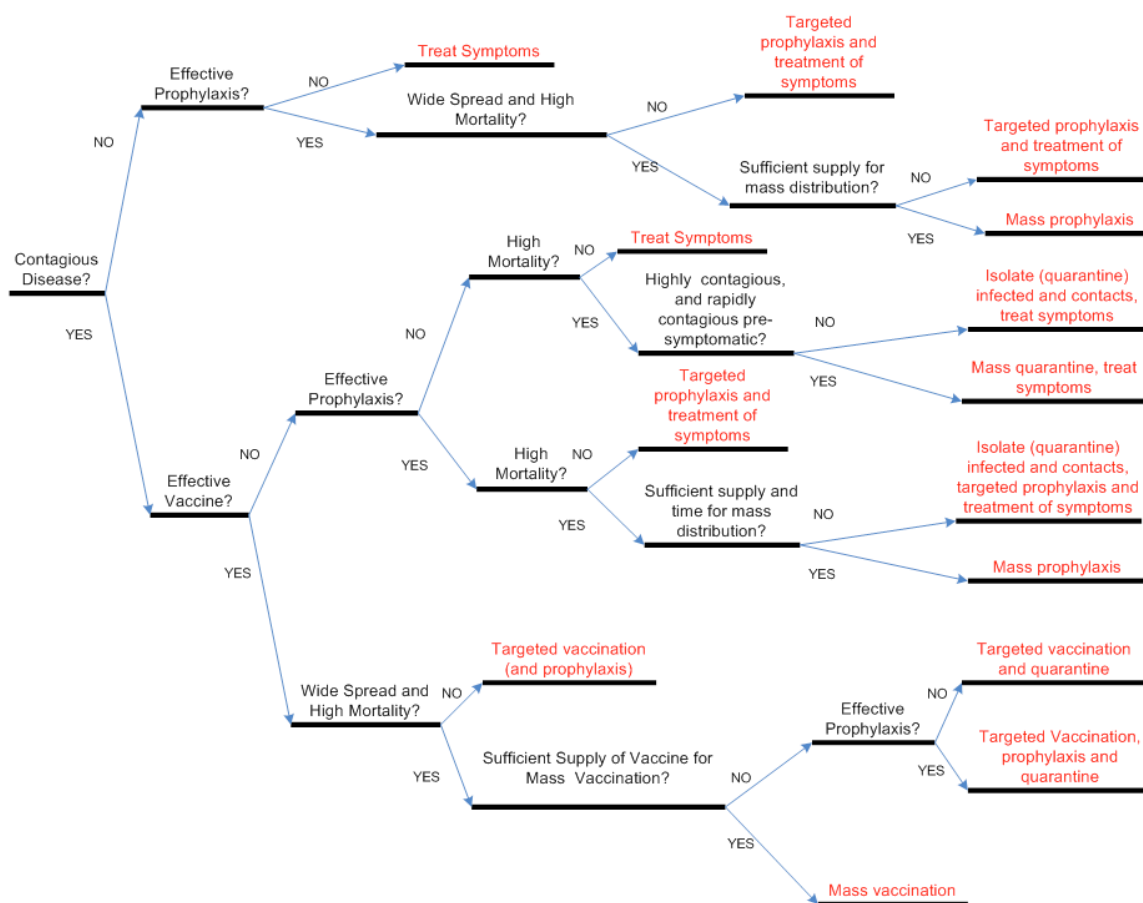
Figure 2.2-1. Decision tree illustrating treatment options depending upon disease and response parameters. Red text indicates treatment strategies.

The decision tree only shows the highest level of the decision space. The details of the decision include where and when the targeted vaccination, prophylaxis and quarantine strategies should be instituted, as well as what individuals or groups should be included in the actions to contain and delay the disease spread. Analyses presented in this report address strategies to contain and delay the spread of a pandemic strain of influenza, and potential impact of containment strategies on further treatment capacity (e.g, tamiflu can be used as a prophylaxis (prevention) or in treatment to reduce symptoms). In the exercise scenario, antiviral use is limited to treatment due to limited supplies.

The decision trees illustrated below, Figures 2.2-2 and 2.2-3, show a type of logical structure that can be used to guide potential courses of action and required decisions. These example illustrations encompass the initial recognition of the disease and initial containment strategy decision points. Ideally, this type of analysis is a logical framework that illustrates how policy decisions and events are inter-related, the circumstances under which a particular decision would be most

favorable, and the future events that may be impacted by a decision. It should be recognized that the best course of action undergoes changes as the scenario progresses, and that there may be no perfect solution, only a least detrimental action. In practice, the information that would be needed to construct decision trees for a composite of policy decisions can be intractable.
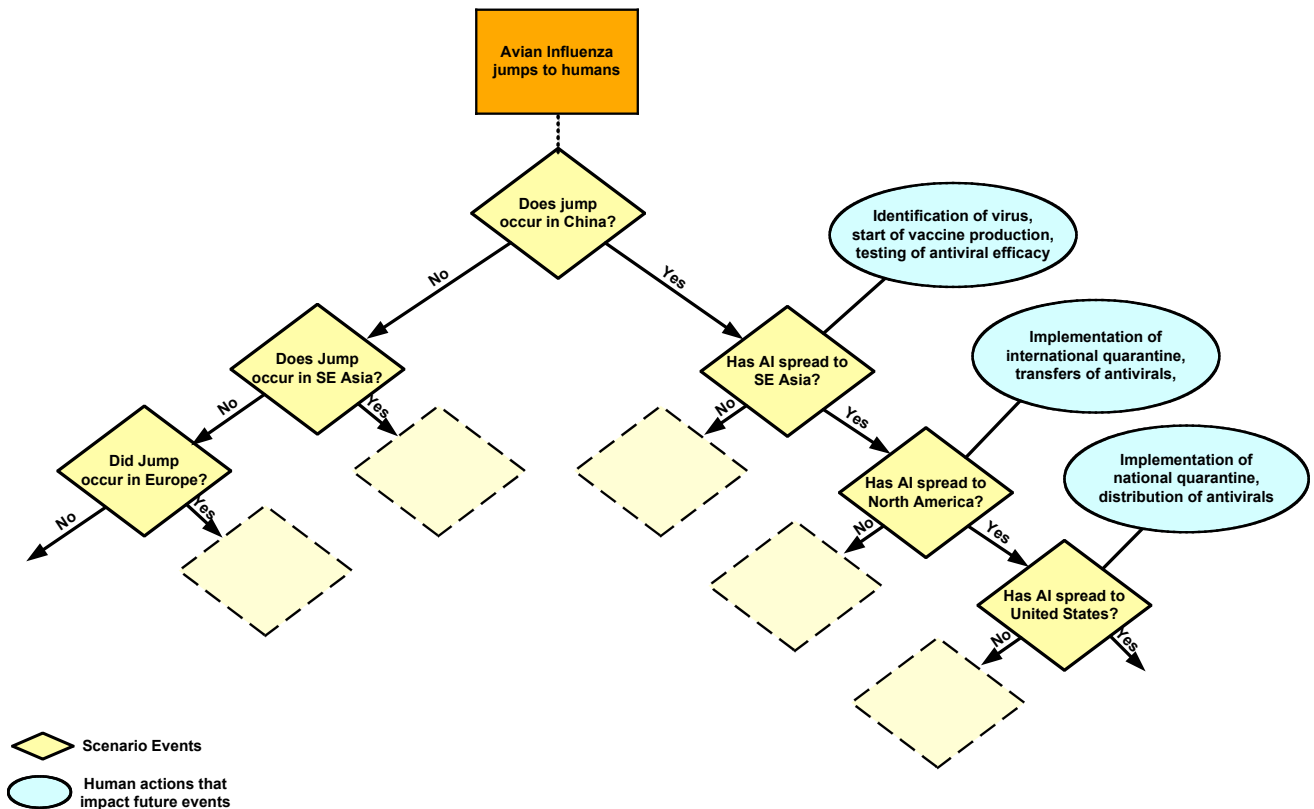
Figure 2.2-2. Decision tree for initiation of pandemic. Diamonds represent the events of the scenario, dashed line diamonds show potential continuation paths for the scenario. Ovals contain human actions and interventions that affect future events. Boxes are initiating actions or events.
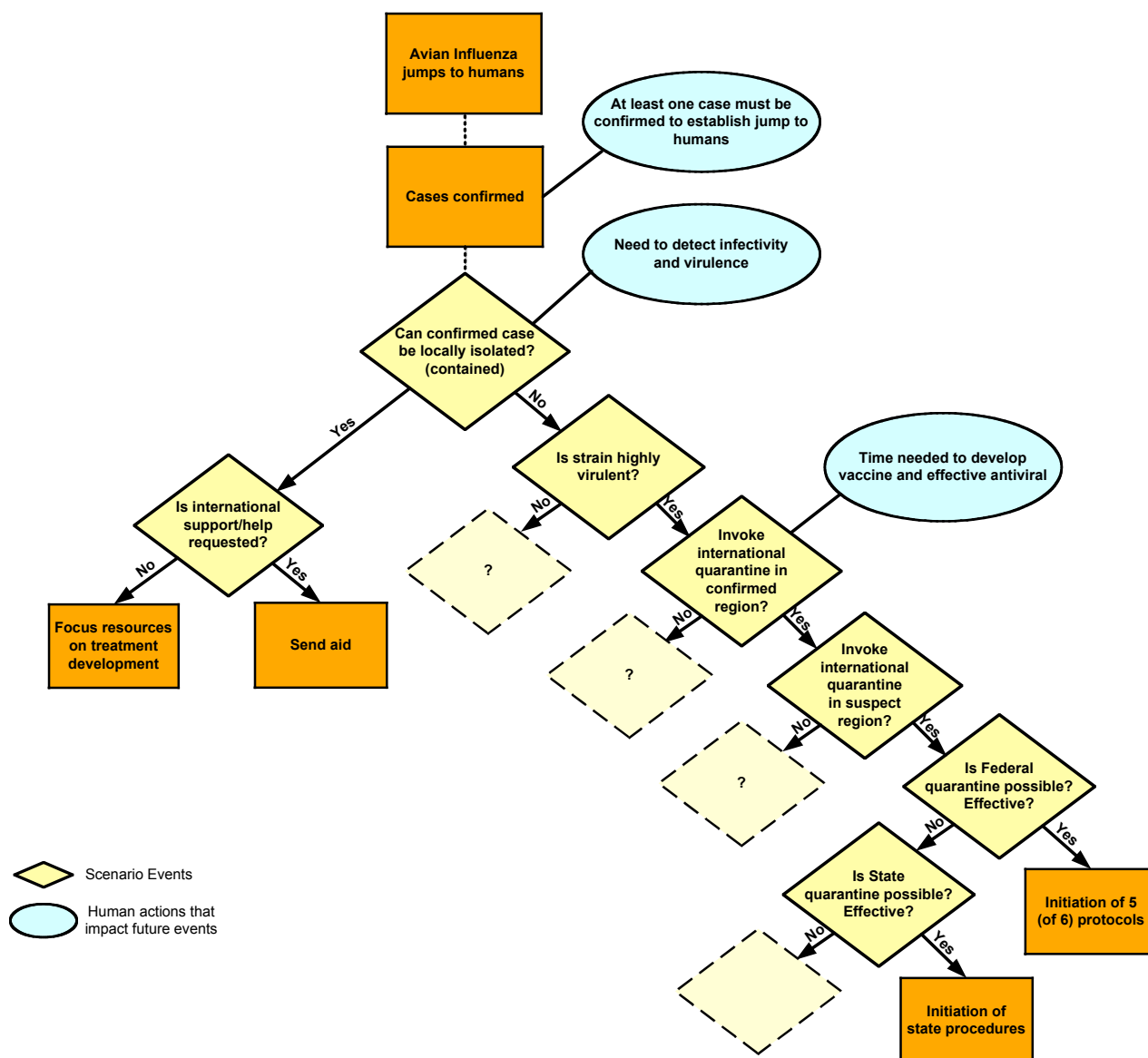
Figure 2.2-3. Decision tree for initial containment strategy. Diamonds represent the events of the scenario, dashed line diamonds show potential continuation paths for the scenario. Ovals contain human actions and interventions that affect future events. Boxes are initiating actions or events.

2.3 Frequently Asked Questions

The terminology used in discussions of a potential avian influenza pandemic can be ambiguous or even contradictory depending upon the source. A glossary is provided in Appendix A to provide detailed descriptions of terms used here.

Appendix B provides information on the status and efficacy of antiviral treatments and Influenza A H5N1 vaccines.

A historical view of case fatality rates for previous influenza pandemics, and the application of these rates to the current potential pandemics are discussed in Appendix C.

In preparation of this report, information was obtained in many areas which provides background significant to issues raised in the scenario. Much of this information is contained in the FAQ below.

What is the difference between an influenza pandemic and an influenza epidemic?

A flu epidemic is a period of excess mortality common to a regionalized (localized) population and typically caused by an influenza sub-type that is already in the human population such as H3N2. A flu pandemic is a global outbreak in the human population, usually caused by a new and virulent sub-type such as H5N1.

The severity of disease and the number of deaths caused by a pandemic virus vary greatly, and cannot be known prior to the emergence of the virus. Based on past experience, a second wave of global spread should be anticipated within a year of the initial outbreak.

As all countries are likely to experience emergency conditions during a pandemic, opportunities for inter-country assistance, as seen during natural disasters or localized disease outbreaks, may be curtailed once international spread has begun and governments focus on protecting domestic populations.

More available at:
http://www.who.int/csr/disease/avian_influenza/avian_faqs/en/index.html

Who (what age groups) might be attacked by an outbreak of H5N1?

World Health Organization data as of November 9, 2005 shows data consistent with past flu pandemics. Younger adults appear to be at greatest risk for clinical symptoms and mortality, as seen in the WHO graph below.

**Human Avian Influenza A/H5N1 Cases
by Outcome and Age Group**
(29 November 2005)
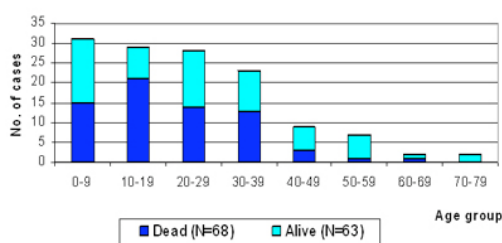
- As of 29 November, total of 133 cases were reported officially to WHO
- 131 cases with available data were included

Will immune system boosters or immunosuppressants be helpful or harmful?

Unknown. Many of the 1918 pandemic deaths were not the result of the flu, but of the body's immune response to the infection.

What may be the incubation period of Avian Flu in humans?

The incubation period of influenza type A viruses is usually short; most infections (symptoms) appear after 1 to 4 days (2 days is typical).

What impacts would uncertainty in the incubation period of Avian Flu in humans have on pandemic spread?

The longer the pre-symptomatic period, the greater the opportunity for spreading the infection, and the greater the difficulty in controlling the pandemic.

What is the difference between isolation and quarantine?

Isolation refers to the separation of persons who have a specific infectious illness from those who are healthy and the restriction of their movement to stop the spread of that illness.

Quarantine, in contrast, generally refers to the separation and restriction of movement of persons who, while not yet ill, have been exposed to an infectious agent and therefore may become infectious.

Why are control strategies that worked for SARS unlikely to work on H5N1?

In contrast to type A influenza viruses, the SARS virus is not contagious before the onset of symptoms and appears to be most contagious 7 to 8 days following the onset of symptoms (Mermel, L. A, Pandemic Avian Influenza, The Lancet, Vol. 5, November 2005). Ill SAR's patients can be detected and isolated while there is still a low probability of infecting others.

What are the main strategies to limit transmission of Avian Flu in humans in the absence of adequate vaccines and supplies of anti-virals?

The two main strategies for prevention of transmission involve

- Decreasing contact between infected and uninfected persons; and
- Decreasing the probability that contact will result in infection.

What are some of the measures that can be adopted to limit transmission of Avian Flu in humans? How effective will these measures be?

- Limits on travel to areas where a novel influenza strain exists
- Screening travelers for symptoms on return
- Canceling of meetings and large group gatherings
- Close schools
- Telecommuting
- Limit availability of public transportation
- Avoiding unnecessary visits to hospitals
- Discouraging hand shaking
- Public education
- Early quarantine of contacts with suspected cases and suspected cases
- Hand washing
- Wearing masks in public
- Antiviral chemoprophylaxis or vaccination if available.

The effectiveness of these measures during a flu pandemic is unknown.

How can citizens feel that they are doing something to prepare, and is this important?

Human behavior studies have shown that active participation reduces panic behaviors in disrupted populations. The citizenry can be instructed to take both protective and preparatory actions. Examples of protective actions include obtaining functional masks and disinfectants. Examples of preparatory actions include the types of actions associated with preparing for any national emergency – stocking up on water and canned goods in case people are homebound due to implementation of quarantine, isolation, or social distancing policies.

3   Scenario and Insights into Policy Issues

Key scenario events, and their decision and discussion points, are summarized below. The scenario events and policy issues with potential courses of action are taken from "Pandemic Influenza Scenario_CATF_1 revised.doc" and "CATF DESIGN-6.doc." For each policy issue, we attempt to provide insights drawn from the analyses given in the remainder of this document.

3.1 Emergence of a Pandemic Virus – Origin and Initial Spread

3.1.1 Scenario Summary

On December 3, a respiratory illness breaks out in a small village in Southeast Asia. The World Health Organization has announces the identification of a sustained human-to-human strain of the H5N1 virus, with uncertainty about where the virus originated. Southeast Asian nations request assistance in the form of antiviral medications from the U.S. and the international community.

3.1.2 Discussion of Policy Issues

3.1.2.1 Policy Issues for Move One

The first two columns of the table below show the policy issues anticipated to be discussed during the tabletop exercise. The third column includes our summary discussion of information relevant to potential courses of action. Policy issues that are outside the purview of NISAC analyses are marked N/A.

Policy Issues	Potential Courses of Action	Discussion
Should the United States and international partners send Tamiflu and other anti-virals from their national stockpiles to Asia in an effort to contain or slow an international outbreak?	1. All-out effort to contain/slow outbreak in Asia through countermeasure deployment, with sustained U.S. leadership and massive assistance 2. Bilateral assistance program with select Asian countries based on quality of political relationship 3. Refer the issue to the WHO or UN for further discussion to see if there is a consensus 4. Reject the idea	The key to effective antiviral policy is administration within a very short window of time. If this cannot be effected, containment is highly improbable. Note - a scenario assumption is that the outbreak can be contained. Published estimates indicate 3 million courses of antivirals will be needed to stop disease assuming a single point source. WHO is in the process of assembling this stockpile.
What, if any, steps will the US take to restrict, discourage, and/or encourage *international* movement to and from other countries or regions … a) where cases have been confirmed; b) where cases are suspected; c) whose governments have implemented unilateral movement restrictions; d) in response to unilateral	1. No federal action; passivity in face of private-sector decisions to cancel flights, etc; passivity in face of international decisions to cancel flights, close borders, etc 2. Provide Tamiflu and anti-virals to aircrews to encourage continued operations of international flights 3. Cancel in-bound flights from countries/regions with confirmed/suspected cases 4. Implement federal involuntary quarantine, medical screening of people from countries with confirmed/suspected cases	A scenario assumption is that the illness will not be kept out of the US. This assumption is supported by analyses in this document. Some strategies of entry restriction may delay the peak onset of infection, providing more time for antiviral and vaccine production. However, the time delays are on the order of days to at most weeks. I The most exacting of restrictions will still not stop entry of such a virus.

e) action by private-sector entities (e.g., airlines, unions, passengers); or in response to politically significant domestic calls (e.g., large city mayor or governor) for international movement restrictions.	5. Support/oppose state involuntary quarantine, medical screening of people from countries with confirmed/suspected cases 6. Implement national effort to people from affected areas that came in over last n days	Economic impacts and social and infrastructure disruptions must be considered for each of the suggested courses of action.
How can the United States and its international partners improve their situational awareness of the spread of the virus?	1. Implement *voluntary* medical screening at U.S. points of entry 2. Implement *involuntary* medical screening, and detention, at U.S. points of entry 3. Coordinate medical screening procedures at U.S. points of entry with international partners 4. Implement national effort to people from affected areas that came in over last n days 5. Deploy international medical teams to regions where infection is present or suspected; when opposed by national government, apply international political pressure 6. Provide technical assistance to countries affected or likely to be affected by the virus	If may feasible to require rigorous reporting from for all nations based on mutual benefit. Financial/economic incentives for action and consequences for inaction might promote compliance. Sick people probably won't self-identify and well people who might be carriers don't know to self identify so voluntary screening seems likely to be ineffective.
What measures can the US and its international partners take to stimulate and accelerate the acquisition of medical countermeasures to Avian influenza?	1. Negotiate with Roche 2. Direct Roche to release production details to generic pharmaceutical producers 3. Release Tamiflu production details possessed by FDA 4. Using the Defense Production Act, the Administration requires the production of Tamiflu by all available firms 5. The Administration initiates voluntary incentives for production 6. The administration absorbs all production liability	If and only if Tamiflu works, then the proposed actions make sense with preference for voluntary compliance.

3.2 Regional and International Spread with First US Cases

3.2.1 Scenario Summary

The H5N1 virus has spread out of Southeast Asia and reached countries throughout the world. Increasing infections and deaths are reported in Asia, and the virus has spread to major municipalities and regions throughout the world. The virus has appeared in the U.S., with 65 deaths reported and domestic tensions on the rise.

3.2.2 Discussion of Policy Issues

3.2.2.1 Policy Issues for Move Two

The first two columns of the table below show the policy issues anticipated to be discussed during the tabletop exercise. The third column includes our discussion information relevant to potential courses of action. Policy issues that are outside the purview of NISAC analyses are marked N/A.

Policy Issues	Potential Courses of Action	Discussion
Who speaks definitely for the U.S. government on matters related to the U.S. response to the crisis? (Is it issue dependent?) What is the message to the private sector and individuals?	1. The President is in charge, speaks for the government (HS Advisor proxy) 2. Sec DHS on all matters 3. Sec DHS with ad hoc delegation to Sec HHS and others 4. Sec HHS	N/A
What actions, if any, should the Department of Defense take to maintain the combat readiness of U.S. military forces?	1. Impose daily mandatory surveillance and quarantine 2. Prioritize Tamiflu and available vaccines to exposed forces 3. Immediately lock down all bases	N/A
Should the federal government accede to a gubernatorial request to support an involuntary quarantine of an identified group of citizens and, if so, provide the personnel needed to carry out this action. If so, which agency to lead this action and with which assets?	1. Fed government supports explicit request with DHS lead and Fed/state enforcement 2. Fed government supports explicit request with HHS lead and fed/state enforcement 3. Fed government supports explicit request with HHS lead and DoD enforcement 4. Fed government intervenes in absence of request or uncooperative state government with Fed officers/DOD support	Analyses should be conducted as to the efficacy of these measures under specific conditions so that when questions arise, productive, informed responses can be immediately implemented. For long-term quarantine, or self-quarantine, issues such as public access to needed or required goods and services are addressed.
What actions should the Federal government take to stabilize the economy? Should the government halt trading in the major U.S. based financial markets?	1. Fed government halts trading in affected industries 2. Fed government halts all trading 3. Fed government does nothing re trading 4. Freeze layoffs in affected industries (government compensates)	Lacking a coordinated international economic response, instability will result. Consequences must be recognized as impacting more than a small set of "affected industries." Trading freezes may shore up falling dollar values, but will probably not make goods and services more available.

What, if any, steps should the federal government take to restrict, discourage, and/or encourage *domestic* movement to, from, and within cities, states, and regions … a) where cases have been confirmed; b) where cases are suspected; c) whose governments have suggested or implemented unilateral movement restrictions; d) in response to unilateral action by private-sector entities (e.g., airlines, Amtrak, trucking companies, barge companies); or e) in response to domestic calls for movement restrictions/unilateral state actions.	1. Impose national holiday for non essential personnel, schools, etc. Fed government overrides any and all unilateral state policy. 2. Impose national holiday *and* discourage movement of non-essential travel. 3. Impose national holiday and ban non-essential travel, enforced by DoD. 4. Fed gov't passivity; state decision	National holiday for some denies goods and services to others. Media can be helpful or harmful in promoting a measured response to avoid panic and excess self-quarantine. Have individuals ready for an emergency (food in house) What would the social response be to banning all non-essential travel? Are there already definitions for "essential travel"?
Who, if anyone, should receive and/or begin taking U.S.-controlled Tamiflu (or other anti-virals) at this time? What public advice or requests, if any, should the U.S. government offer with respect to non-U.S. controlled Tamiflu (or other anti-virals)? What steps, if any, should the federal government take to assume control over a greater portion of Tamiflu (or other anti-virals) available inside the United States?	1. Prophylactic use in affected areas to reduce spread 2. Treatment only in all affected cases 3. Prophylactic/treatment reserved for essential personnel Distribution options: 4. Fed government commandeers all countermeasures and distributes with aid of states 5. Fed government allows states to manage distribution	A scenario assumption is that antivirals will be used for treatment and not prophylaxis. Results provided here support this assumption because of the timeliness required for effective use of these drugs. Typical prioritization schemes give highest priority to health care workers. Recognition is needed that effective health care requires infrastructure support from the electric power and transportation sectors, which in turn, rely on other infrastructures in a highly interdependent system. In the absence of sufficient antivirals or vaccines for essential workers, alternative strategies such as telecommuting and protective personal equipment may be effective.

3.2.2.2 Discussion of Policy Issues: Quarantine and Entry Restrictions on Arriving International Travelers

A policy issue central to this table-top exercise is whether quarantine, travel restriction, or other methods of reducing the rate of arrival of infected international travelers from infected locales can reduce the impact of an influenza pandemic. Two general approaches are considered: prevention of symptomatic travelers from entering the US, and travel restrictions to reduce the number of arrivals coming from infected regions. The NISAC EpiSimS model has been used to quantify the efficacy of these approaches to mitigate or delay an epidemic in the US.

Infected travelers in the latent-incubating stage, as well as infected travelers with sub-clinical manifestations, can not be distinguished from uninfected persons through observation of symptoms. Non-symptomatic infected travelers will account for 70% of the infectious source from international travelers. A policy of quarantining symptomatic international arriving travelers could at best reduce the infectious source by 30%. Based on analysis calibrated to EpiSimS simulations, such a policy would delay the US epidemic by about 5 days.

For the planning scenario pandemics, in which 25%-40% of the population would be infected in the absence of national-scale vaccine or antiviral treatment programs, the arrival of only 10 infected persons would practically ensure an epidemic in the US. For unrestricted entry of international travelers, 10 infected persons will have arrived to the US by the time that the prevalence in the source region reaches 0.12%. If symptomatic persons are prevented from entering, 10 effective infected persons would have arrived to the US when the source region prevalence reaches 0.18 (i.e. 5 days later). These levels of prevalence are expected to be reached in the source region some four months after the transition to human-to-human transmission.

A second quarantine strategy would, in addition to preventing entry of all symptomatic persons, reduce the total number of travelers originating in regions in early epidemic stage. The strategy would account for 1) population of infected region, 2) fraction of population in infected region that normally enters the US each day, and 3) the epidemic prevalence. When the product of the above three factors reaches a triggering threshold, a travel restriction policy would be emplaced to reduce the number of travelers from the infected region. The triggering threshold might be 0.05 expected infected travelers per day, for the first infected region of a pandemic. Later in the pandemic, when there are many infected regions in the world, the threshold might be lowered to 0.01 (or less) expected infected travelers per day from a particular infected region.

The degree to which travel can be restricted will depend on many unknowns, so the allowed fraction of travelers from infected regions is parameterized over the values {1.0, 0.5, 0.1, and 0.02}. The respective delays in the US epidemic would be {4.9 days, 14.5 days, 37 days, and 59 days}. Entry restriction could provide a month or two of delay in the US epidemic if travel can be restricted by a factor of ten or fifty from infected regions during the early growth stage of their

epidemic. This delay could prove invaluable in allowing time for development of effective vaccine. However, we find that even a 50-fold reduction in international arrivals would be unlikely to prevent a US epidemic during a global pandemic.

3.3 Pandemic scenario – Spread and Impacts of Pandemic Disease in the U.S.

3.3.1 Scenario Summary

The flu has flooded into the U.S. population with over 65,000 dead and millions verifiably infected or at least exhibiting symptoms. Confusion and lack of coordination between municipalities, states, and the federal government have resulted in an uneven response.   The result has been widespread looting, hospital overcrowding, and civil unrest in the developing world.

3.3.2 Discussion of Policy Issues

3.3.2.1 Policy Issues for Move Three

The first two columns of the table below show the policy issues anticipated to be discussed during the tabletop exercise. The third column includes our discussion information relevant to potential courses of action. Policy issues that are outside the purview of NISAC analyses are marked N/A.

Policy Issues	Potential Courses of Action	Discussion
Should the federal government act to bring order to United States where there is a gubernatorial request to do so? Which agency should lead this effort? Should the federal government act to bring order to U.S. city in absence of gubernatorial request to do so? Which agency should lead this effort?	Requesting cities 1. DOD lead with Title 10 active duty troops 2. DOD lead in conjunction with Governors and title 32 troops 3. DHS lead in conjunction with Governors and title 32 national guard Non-requesting cities 1. Unilateral action (1,2,3 above) 2. Intense pressure on Governor and Mayor to address	N/A
Should the federal government nationalize, take over, or directly provide key transportation	1. Nationalize airlines and critical transportations systems; DOT manage	If people don't show up for work, it doesn't matter who's the boss.

services? Who should manage this? With what resources, capabilities, and authorities?	Federal system 2. Nationalize airline and critical transportation, DOD manage 3. Support private sector efforts with safety and supplemental personnel	Does the government have enough personnel, and resources to make this happen? Would there be added costs for shifting these government workers (aren't these union employees)? What would industry's long-term response be?
What steps should the Federal government take to enhance health response? Should the federal government nationalize, take over, or indemnify, or directly provide key health delivery services? Who should manage this? With what resources, capabilities, and authorities?	1. Indemnify health care providers to allow free flow of medical staff to areas of need 2. Nationalize facilities in intensely affected areas and provide DOD health staff	The root of why people are not going to work (for example lack of child care/open schools) may be more important to address than leadership questions. Are there enough people to do the job? Coordination of local and voluntary efforts and health care supply chains is of paramount importance.
What further limitations should be placed on movement of persons and trade goods?	1. Ban all movement between cities and states 2. Declare nationwide and region wide snow days 3. Provide guidance but allow state and local decisions	From public perception point of view, would need to demonstrate benefits, i.e. by what factor would spread rate be reduced / what would be time lag (results provided in this document suggest minimum effectiveness of implementing limitations).

3.3.2.2 Discussion of Policy Issues: Impact of Partially-effective Vaccine Becoming Available Part Way Into the Epidemic

A critical policy issue relating to the fully-established pandemic stage (table-top move 3) is the implementation of a massive program of vaccine development. The particular questions of interest concern the relative benefits of early production of less-effective vaccine versus later production of more-effective vaccine. The analysis section describes a quantitative analysis of the dynamics of an epidemic with partially effective vaccine becoming available part-way into the epidemic conducted with the simulation tool EpiSimS. The salient policy issues regarding the crash vaccine development policy are discussed here.

A base-case epidemic was computed with EpiSimS, for the scenario with no vaccine or antiviral treatments are available. For the base-case scenario, 26% of the population is infected (including sub-clinical manifestations) and 1.3% of infections are fatal.

The vaccine used against normal epidemic influenza is taken as the benchmark for nominal effectiveness. This vaccine produces immunity in 70% of treated individuals. In addition, in the 30% of vaccinated individuals that remain susceptible to infection, the course of the infectious period is shortened by an average of one day, and the infectiousness during the infectious stage is reduced by 80%. A partially-effective vaccine is taken to be half as effective as this nominal benchmark effectiveness. Thus the partially effective vaccine would produce immunity in 35% of treated individuals, reduce the average infectious period by 0.5 days, and reduce the infectiousness during the infectious stage by 40%.

EpiSimS simulations were executed with four different vaccine availability times, for partially and fully effective vaccine. The four starting times are: early in the epidemic (when there are 200 cases), four weeks before the epidemic peak, at the epidemic peak, and four weeks after the epidemic peak.

The partially-effective vaccine delivered early in the epidemic reduces the attack rate (i.e. the fraction of the population that gets infected) from 26% to 0.2%, essentially preventing the epidemic. If the partially-effective vaccine could not be delivered until four weeks after the epidemic peak, the attack rate reduction would only be from 26% to 24.6%. As long as it is delivered early, the partially-effective vaccine is as powerful as the nominally-effective vaccine. Early identification of influenza cases and timely vaccine manufacturing is crucial in limiting the size and length of an outbreak.

Another critical policy issue is the amount of vaccine that should be planned. To illuminate this issue, EpiSimS was used to evaluate a range of vaccine availability levels: vaccine available for everyone, for 40% of the population, and for 20% of the population. For the 20% availability level, the CDC recommendations are followed that the vaccine is targeted preferentially to children, elderly persons, and persons with underlying medical conditions. At the 40% availability level, the vaccine is distributed independently of demographics.

Vaccination of 20% of the population early in the epidemic with nominally-effective or partially-effective vaccine reduces the size of the epidemic while increasing the duration of the epidemic. If 20% of the population is vaccinated four weeks prior to the epidemic peak, the epidemic attack rate would drop to 13.2% for partially-effective vaccine and 12.3% for nominally-effective vaccine. A further four week delay (vaccine not available until the epidemic peak) give attack rates of 20.7% and 19.0%, respectively. If the vaccine is not available

until four weeks after the peak, the vaccine would only cut the attack rate from 26% down to 25%. Early production of less-effective vaccine would provide better consequence mitigation than later production of more-effective vaccine.

The currently available antivirals have proven to be effective in preventing infection, reducing symptoms, shortening the infectious period, and reducing the probability of transmission. However, it may be that existing antivirals are not as effective against future pandemic flu virus. EpiSimS has been used to evaluate a partially effective antiviral treatment, taken to be half as effective as when used against currently circulating influenza strains. To match the Strategic National Stockpile of 5.3 million courses of oseltamivir, we consider an antiviral supply sufficient to treat 2% of the population with a therapeutic or prophylactic course. Antiviral medications are distributed to the population in the following manner: 1) persons with influenza symptoms, and 2) named contacts for such symptomatic persons, in particular individuals in the same household, school, or workplace. The fraction of contacts that are found for the different social settings are: 90% household contacts are found, 90% visiting, 80% work, 80% school, and 50% college.

A ring delivery of partially-effective antivirals stop an influenza pandemic within 42 days (within 21 days for nominally-effective antivirals). EpiSimS results show that timely ring delivery of even partially effective antivirals is more effective than any other intervention analyzed in this study. Although, ring delivery would be hard to implement, given the short incubation period of influenza, under a limited resource scenario, it should be considered. An influenza pandemic may be controlled by means of ring delivery of antivirals, and early distribution of vaccines. Having a pandemic flu vaccine available early in the epidemic is an extremely optimistic assumption for the first wave of the epidemic. Therefore, case isolation, contact tracing, and timely distribution of antiviral seem to be the best strategy in containing a pandemic.

The four most important policy implications from the model results are:

1) Delay in intervention will dramatically increase the total number of cases and deaths.
2) Timely ring delivery of limited antivirals can reduce the number of cases and shorten the epidemic drastically.
3) Partially-effective and nominally-effective vaccines have similar effects in the overall impact of the epidemic: Manufacture of vaccine should not be delayed to obtain incremental improvements in efficacy.
4) A response policy may affect both the number of cases and the duration of the epidemic, possibly requiring careful trade-offs.

3.3.2.3 Discussion of Policy Issues: Consequence Mitigation Strategies on a National Scale

While many models treat epidemic dynamics on a local, city, regional scale, there are major policy issues that can only be examined with high-fidelity analysis at a national scale. EpiCast is an agent-based model for the contiguous United States that captures the transmission of the virus in different mixing groups like community, work-places, household clusters, schools, and households. In this large-scale model the 280 million agents are distributed among 5 age groups according to demographic data. The geographic distribution is represented by about 60,000 US census tracts (each containing about 5000 people) and movement of people between the tracts. The movement is given by data from the transportation bureau and can be split into daily commuter travel to work and longer distance travel (business trips, vacation, etc.). By fitting the model parameters to different aggressive strains –as represented by the basic reproductive number R_0 (basically the number of persons a sick individual infects directly) – several mitigation scenarios for different virus strengths could be investigated.

A variety of mitigation strategies and their combinations are modeled in EpiCast. In addition to mass vaccination and treatment of named contacts of diagnosed cases with antiviral medications, these include the reduction of travel, school closure, non-essential work closure, and other social distancing measures, up to a mandatory quarantine.

Preliminary results suggest that for reproductive numbers R_0 less than 2.0, targeted administration of antiviral drugs helps to control the spread until vaccine is developed. For more aggressive viruses a more sophisticated combination of therapeutic and social distancing measures (including quarantine, school closure, and/or travel restrictions) is necessary to control the spread.

4 Models and Model-Specific Analyses and Results

A suite of computerized models were used to analyze the spread of infectious avian influenza. Individual models rely on different methods and assumptions, but in combination they form a suite of tools useful for looking at different aspects of disease development, spread, and mitigation. The model results show the relative efficacies of different mitigation measures and are presented.

It is important to note that models are based on specific assumptions and artificial communities, and therefore show the relative efficacies of different mitigation measures. There are uncertainties associated with any absolute numerical results.

Once more is known about a disease outbreak and parameters, we may be able to run simulations with more accurate assumptions.

Definitions of terminology are provided in the glossary (Appendix A). Several models use the variable R_0, the basic reproductive number of a disease, which is defined as the average number of secondary cases generated by a typical primary case in a susceptible population.

The models are presented in chronological order relative to the scenario. The model results are summarized in an abbreviated form in Section 4.1, and described in greater detail in Sections 4.2 – 4.7.

4.1 Model Result Summary

The CIP/DSS model and analysis (Section 4.1) examines the effectiveness of implementing travel restrictions for people leaving Southeast Asia. Results show that for the unmitigated case (no travel restraints in either the US or Thailand), the epidemic reaches its peak in the US 29 weeks after the 1st case appears in Thailand. If Thailand curtailed the travel of infected individuals by factor of 200 over the course of a 4-month window (i.e., from 2000/4m to 10/4m), then the peak in the US would be delayed by 3 weeks. Regardless of the rate at which Thailand reduces travel, the pandemic runs its course and there are no reductions in the number of deaths and infected in the US.

EpiHistogram and EpiSimS models (Section 4.2) were used to look at implementation of controls on arriving passengers. Three travel restriction strategies are examined.

- The first strategy quarantines arriving individuals who are symptomatic. Since non-symptomatic infected travelers will account for 70% of the infectious source from international travelers, a policy of quarantining symptomatic international arriving travelers could at best reduce the infectious source by 30%. Results of analyses calibrated to EpiSimS simulations, show that such a policy would delay the US epidemic by about 5 days. This is smaller than the timing variation due to stochastic effects early in the epidemic.
- The second strategy would, in addition to preventing entry of all symptomatic persons, reduce the total number of travelers originating in regions in early epidemic stage. This strategy could provide a month or two of delay in the US epidemic if travel can be restricted by a factor of ten or fifty from infected regions during the early growth stage of their epidemic.
- The third approach looks at regional travel restrictions with a strategy of reducing the number infected people arriving at a city or region from somewhere else in the US. For the example case of Portland, OR cutting the influx of infected travelers from twenty per day to five per day delays the

onset of an epidemic by close to three weeks. Curtailing the infected travelers from ten per day to one per will give an additional 3 week delay.

Strategies for optimally administering vaccines, and strategies for structured social distancing in the absence of effective vaccines and antivirals are examined using the Loki-Infection model in Section 4.3. Loki-Infection is a networked agent-based model that incorporates individual-individual interactions within a multiply overlapping social contact network in a simulated community (10,000 individuals for these analyses). Results include:

- If the vaccine supply is limited, a "children and teenagers first" vaccination strategy could be very effective in thwarting an influenza epidemic. All others within the community would be protected by herd immunity rather than direct vaccination. Model results for the simulated community show that substantial reductions in infection and death rates could be achieved if the vaccine is administered and effective for ~60% of the children and teenagers.

- Similarly, social distancing of "children and teenagers only," could be highly effective in thwarting the spread of infection, especially in the absence of effective vaccines or antivirals. A social distancing policy would require those under 18 years of age to be restricted primarily to their homes for the duration of the epidemic. With this social distancing strategy, adults may continue to work and interact within the community as normal. If implemented quickly within the community (after 10 symptomatic individuals are discovered) and with full compliance, reductions in the number of people who are infected or die are above 97% for the simulated community. If compliance is relaxed to 70% so that children and teenagers maintain 30% of their normal social contacts outside the family, the number of people that are infected or die are still reduced by greater than 84%.

Antiviral usage strategies are examined with the Avian Influenza Discrete Event Simulation model (Section 4.4), which uses a Monte Carlo simulation to investigate the propagation of influenza through a population. Mass and targeted antiviral strategies are examined.

- Model results show that for a mass antiviral policy in the model community, disease transmission rates slow when 55% of the population is provided with antivirals, and the pandemic can be eradicated if that number is increased to 60% or above.

- If antivirals are provided only to contacts (previous, current, and future) of infected individuals, then to reduce the numbers of infected and halt the pandemic, the accuracy of tracing, and the success rate for providing antivirals to contacts within the required time window must be sufficiently high. (The product of accuracy and success must be greater than 0.45 under the model assumptions.) Therefore, the success of the

contact tracing policy depends upon accurate identification of possible infective contacts, and the speed with which antivirals can be distributed.

- If antivirals are provided only to children and teenagers, then the pandemic may be suppressed if the R_0 value for adults is less than 1.4.

The efficacy of vaccination and antiviral strategies was also examined using EpiSimS in Section 4.5. This analysis differs from the Loki-Infection and AI DES analyses in that in this analysis the medications are partially effective, and arrive during, rather than at the start of, the pandemic. The four most important policy implications from the model results are:

- Delay in intervention will dramatically increase the total number of cases and deaths.

- Timely ring delivery of limited antivirals can reduce the number of cases and shorten the epidemic drastically.

- Partially effective vaccines have similar effects in the overall impact of the epidemic; therefore, delaying manufacturing to produce a more effective vaccine may not be worth it.

- Timely targeted vaccination of children and elderly can prolong the epidemic, resulting in a greater economic impact.

This last result might appear contradictory to the results obtained using Loki-Infection. However, Loki-Infection results show that as the vaccination rate in any population (regardless of whether it is children and teenagers or adults) is increased from 0, the time span for the epidemic at first lengthens and then quickly decreases when herd immunity is acquired. In Loki-Infection, which contains an explicit social contact network, the crossover from lengthening to shortening happens at about 45% vaccination of children and teenagers (assuming 100% effectiveness) and herd immunity is acquired at 60%.

Lastly, EpiCast, an agent-based model for the US, was used for a nationwide analysis of consequence mitigation in Section 4.6. These results suggest that:
- For reproductive numbers (R_0)less than 2.0, targeted administration of antiviral drugs helps to control the spread until vaccine is developed, produced, distributed, and has had time to produce an immune response.
- For more aggressive viruses, a more sophisticated combination of therapeutic and social distancing measures (including quarantine, school closure, and/or travel restrictions) is necessary to control the spread.
- Drastic restrictions on nonessential long-distance travel, to as little as 1-10% of the normal rates, were also studied. Although the final attack rate is completely unaffected by such a strategy, it is useful in delaying the spread from the initial sites of introduction to the rest of the country by as much as a month or two, depending on R_0 and the level of travel reductions.

4.2 Combating Early Epidemics Outside the US: Results of CIP/DSS Model

4.2.1 CIP/DSS modeling of epidemic containment

This section presents an analysis of the issues relating to US efforts to combat a pandemic outside the US. This analysis was conducted by the Critical Infrastructure Protection Decision Support System (CIP/DSS) team. The World Health Organization, government leaders, and influenza experts worldwide are concerned that the recent emergence and rapid geographical spread of an avian influenza virus, Influenza A/H5N1, has the potential to go from local epidemic to a global human influenza pandemic. The rapid spread of influenza easily from person-to-person poses the most difficult challenge to designing realistic control strategies and policies. In addition the 24 hour period during the 48 hour incubation period of the infection, when persons are asymptomatic and infectious, proves to increase the difficulty in containing an epidemic.

The basic reproductive number (R_0) of a disease is defined as the average number of secondary cases generated by a typical primary case in a susceptible population. A disease can spread if R_0 is greater than one, and if R_0 is less than one then the epidemic will eventually stop. Therefore the goals of control strategies are to reduce this reproductive number to below one. A Ferguson et al. (2005) point out this reduction in R_0 can be achieved in three main ways: (1) by reducing contact rates in the population through quarantines, (2) reducing the infectiousness of infected individuals through drug treatment and isolation, and (3) by reducing the susceptibility of uninfected individuals. However, even with utilization of all three types of control measures in a region with an epidemic, containment inside that region will be difficult at best.

Currently, there are two published papers that model strategies for containing an influenza pandemic in Thailand (Ferguson et al. 2005 and Longini et al. 2005). Estimating the potential and number of infected persons leaving the epidemic region is important in modeling the impacts of containment of influenza in the region. Longini et al. (2005) estimate the daily probability that an infected person will escape an area is 10^{-3}.

We modeled the incoming persons coming into the United States over four months to mimic the "sparking" of infected persons outside the seed region of concern. To gather a range of numbers for infected persons entering the US from Thailand we used an estimate of infected persons leaving with no control measures in place in Thailand. If the epidemic in Thailand is uncontrolled, then there is a large potential for incoming infectious persons into the United States. The initial seed of infected people arrive from Thailand to the United States over the 7 day period from January 13 to January 20 when the first case in United

States is documented.   All flights from Asia are assumed to be full. As an approximation, we used the following formulation:

(number of Thailand-US flights in one week) X
(number of passenger seats on a Boeing 747) X
(fraction of people from Thailand) X
(expected number of people sick during that week; i.e. 2.5% of population)

There are 14 flights from Thailand to the US per week [1].

There are 524 passenger seats on a Boeing 747 [2].
The prevalence used in the model is 0.025.

We now have a one parameter (N) model, where N is the fraction of people on a given flight that come from the affected region. We vary N from 25%-100%, since most of the passengers are probably coming from Thailand. Using these parameters we obtain:

14 * 524 * N * 0.025 which gives us a range of 46-183 infected people arriving in that 7 day window when the peak epidemic is occurring in Thailand and prevalence levels are high enough for maintaining infected escapees to leave. If everyone on the planes from Thailand is from Thailand, the 183 infected arrivals per week translates to 2000 infected persons over a four month period entering the United States.

To simulate control measures in place in Thailand we reduced the number of infected persons to the United States over a four month period sequentially from 2000 down to 10 infected persons or roughly one infected person per week.

4.2.2 Results

A combination of control measures that includes all of the three types of control strategies in the country of Thailand produces a 200 fold reduction in the epidemic in Thailand, allowing approximately one infected person into the United States per week over the four months. In the base case scenario of no control measures in place in the United States, there was no delay in the initial numbers of infected in the first initial days of the new epidemic. However, there was a delay in when the peak infection growth period of three weeks between the two extreme cases.   With no control measures in place an epidemic would occur in the United States with no significant differences in total cases or mortality for having control measures in place in Thailand, greatly reducing the number of infected persons leaving the county.

Once a strain is identified most evidence suggests a three to four month period to get top vaccine capability.   New vaccine facilities are estimated to cost 150

million dollars. Once the correct strain is identified and the facility is in top production, the number of vaccines produced ranges from 0.72 million for the trivalent vaccine to 13 millions doses of adjuvant-added vaccine per day. However, due to the rapid spread of influenza and the resulting epidemics across the world, it is critical that this time period be shortened. In this scenario, the epidemic in the United States does not hit its peak growth period until 29 weeks after the initial case in Thailand with control measures in place. However, it reaches it peak in the United States two weeks earlier if no control measures are taken. If peak vaccine production is occurring at that time, 182 million doses of adjuvant H5N1 vaccines could be made in that time period.
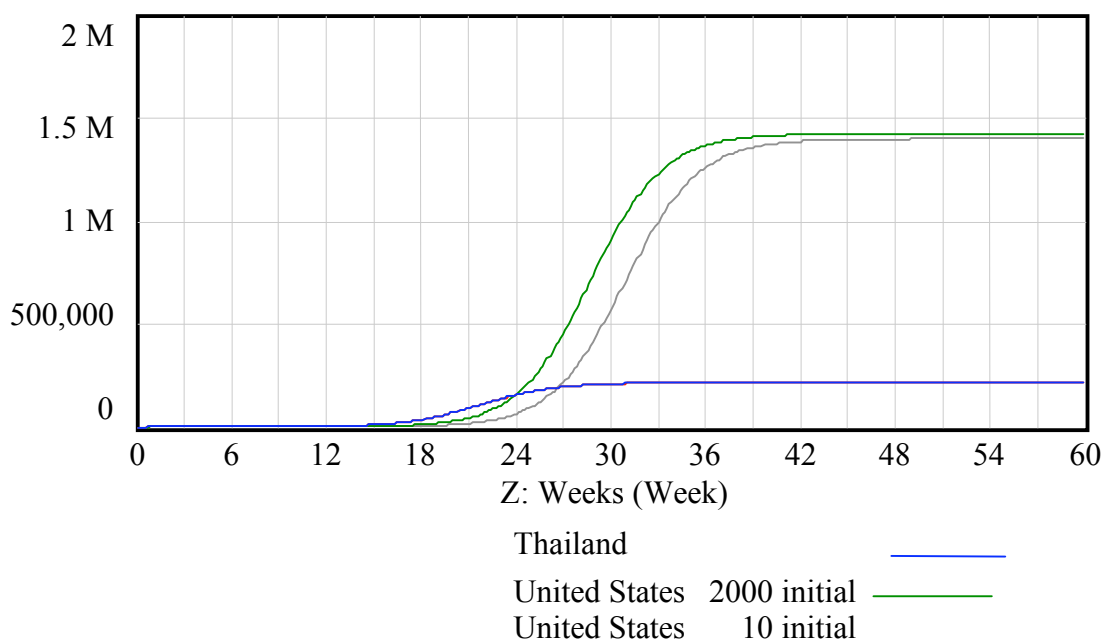
Figure 4.2-1. Mortality in the United States for 2000 infected travelers arriving from Thailand over four months, and for the arrivals reduced to 10 infected travelers over four months due to mitigation efforts in Thailand.

Total Cumulative Cases by Region
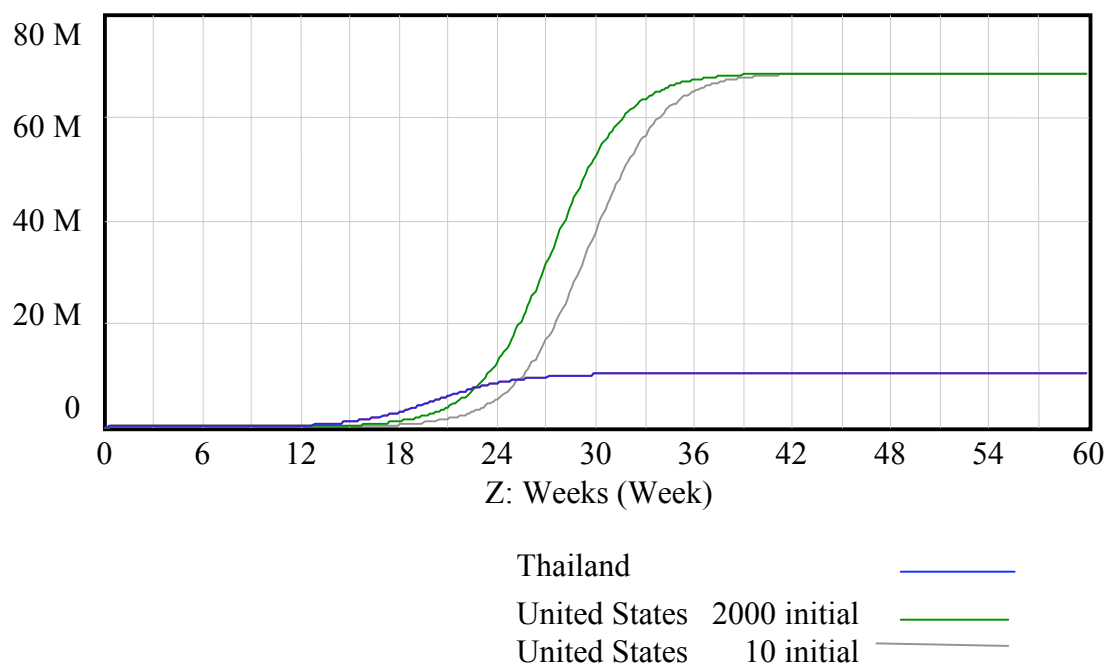
Figure 4.2-2. Total influenza cases in the United States for 2000 infected travelers arriving from Thailand over four months, and for the arrivals reduced to 10 infected travelers over four months due to mitigation efforts in Thailand.

4.3 Impact of Entry Restrictions for Arriving International Travelers: EpiHistogram/EpiSimS Modeling

4.3.1 Extension of EpiSimS model via EpiHistogram to Evaluate Travel Restrictions

In this section, we address the question of whether quarantine, travel restriction, or other methods of reducing the rate of arrival of infected international travelers from infected locales can reduce the impact of an influenza pandemic. The analysis is performed with the NISAC tool EpiHistogram, which is used to extend EpiSimS simulations to regions that have not been characterized with high-fidelity demographic and mobility data.

US law provides that captains and crews of ships and airplanes report passengers with any of nine diseases[1] to local authorities at point of destination. Existing law regarding quarantine of sick arriving international travelers is under reevaluation due to the current elevated likelihood of emergence of avian-related pandemic

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[1] Cholera, diphtheria, tuberculosis, plague, smallpox, yellow fever, viral hemorrhagic fever, SARS, and pandemic-type influenza.

influenza. NISAC epidemic dynamics simulation tools have been used to quantify the efficacy of quarantine or travel restrictions to reduce the number of arriving infected persons to mitigate or delay an epidemic in the US.

Infected travelers in the latent-incubating stage, as well as infected travelers with sub-clinical manifestations, can not be distinguished from uninfected persons through observation of symptoms. In the following analysis, it is found that non-symptomatic infected travelers will account for 70% of the infectious source from international travelers. Only 30% of the infectious source can be attributed to symptomatic infected travelers. A policy of quarantining symptomatic international arriving travelers could at best reduce the infectious source by 30%. Based on analysis calibrated to EpiSimS simulations, such a policy would delay the US epidemic by about 5 days. This is smaller than the timing variation due to stochastic effects early in the epidemic.

It is supposed that a global pandemic will begin with a major epidemic in a particular region of the world. Epidemics would then be initiated at various times in other regions of the world through movement of infected travelers. For this table-top exercise, the initial epidemic is presumed to occur in south-east Asia, in particular, in the nations of Thailand, Burma, and Cambodia.

Several epidemic modeling tools have been developed to enable rapid exploration of underlying scientific issues relating to EpiSimS, and to extend, interpolate and interpret EpiSimS results. This set of tools is collectively called *EpiScope*. Two *EpiScope* tools, *EpiHistogram* and *EpiC*, were used in this analysis. *EpiHistogram* is a quick-running deterministic epidemic dynamics model that has been calibrated to both *EpiSimS* and *EpiCast* simulations. *EpiHistogram* was originally developed to determine what R_0 value best characterizes the result of an EpiSimS simulation. It has been used here to estimate the progression of an initial epidemic in SE Asia. The *EpiHistogram* model implements:

1) data-based histograms giving the distribution of incubation-stage and infectious-stage sojourn times at half-day resolution,

2) Convolution of new case rate with incubation time histogram to give new symptomatic rate

3) Convolution of new symptomatic rate with infectious time histogram to give removal rate

4) Eulerian integration with 5000 timesteps (e.g. 250 days at 0.05 day timestep),

5) New infections per timestep computed with power-law mixing model calibrated to high-fidelity multi-million-person EpiSimS simulations.

EpiC is a GUI-driven java application that implements an agent-based representation of individuals interacting in four levels of mixing groups, and the histogram-based disease stage transition model. Epidemic dynamics are implemented stochastically with a discrete event engine that maintains a priority

queue of disease transmission events. *EpiC* has been calibrated on the widely referenced 2000 person structured community model of Longini, as well as to *EpiSimS* and *EpiCast* simulations. *EpiC* was used to compute the likelihood that an epidemic fizzles, as a function of the number of index cases. For epidemic parameters leading to a 25% attack rate, it was found that with 10 index cases, the likelihood of a fizzle is less than 0.1%. This is independent of whether the index cases arrive at one time or are widely spread out in time. In addition, EpiC was used to explore the stochastic effects that produce variation in the timing of the onset of the exponential growth stage of an epidemic. For epidemic parameters leading to a 25% attack rate, a 16 day standard deviation is seen in the time of epidemic onset (e.g. the time at which a level of 50,000 infections have been reached) in an ensemble of 1000 simulated epidemics.

The combined population of the source region (Burma, Thailand, and Cambodia) was set to 162 million. The transmission is computed with a power-law mixing coefficient of 2.18, which was observed in EpiSimS simulation of epidemics in Los Angeles[2]. The basic reproductive (R_0) rate was adjusted to a value of 1.34 in order to obtain a planning scenario attack rate of 23.5%. The computed prevalence, f (i.e. the fraction of the population that is sick, including those in the incubation stage and those with sub-clinical manifestations), as a function of time is shown in Fig. 4.3-1. The epidemic reaches a peak prevalence of 2.51%. During the early part of the epidemic, the number of new infections per day grows approximately exponentially, with a growth rate coefficient of 7.2% per day. The epidemic takes 49 days to go from half peak to peak and back down to half peak rates. 80% of all cases occur in a period of 61.5 days.

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[2] This power-law transmission model gives the number of new cases per day as (R_0 / 4.1 days) (# remaining susceptibles / initial population)$^{2.18}$.
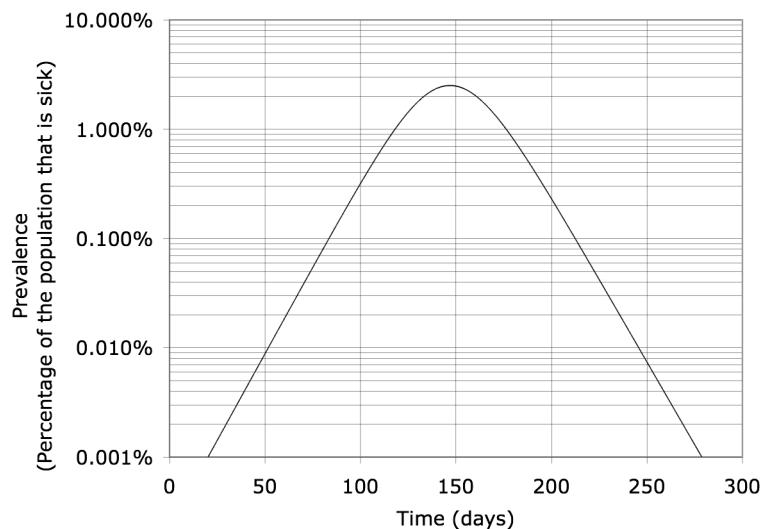
Fig.4.3-1. The fraction, f, of the population that is sick, in the region of the world in which the pandemic originates, for a avian-related influenza pandemic typical of planning scenarios (23.5% attack rate), calibrated to EpiSimS simulations.

The DHS CPB reports that during FY2005, 86 million air passengers were cleared for entry into the US. An additional 26 million arrived on ships, but these are primarily cruise ship passengers and so do not represent international travelers. Counting only international air travelers gives an average of 220,000 arriving international travelers per day. The combined population of Burma, Thailand, and Cambodia is 162M, that of the world is 6446M, and that of the US is 296M (Jul 2005). If the number of international arrivals is simply proportional to the population of the place-of-origin, 5800 persons per day would be entering the US from these three SE Asian countries. Because of remoteness and other cultural factors, this estimate is reduced to 1000 people per day arriving to the US from the source region.

4.3.2 Quarantine Strategy 1: Prevent Entry of Symptomatic Travelers

The infected people in the source region can be placed into five categories as enumerated in Table 4.3-1. The first column gives the fraction of cases in the source region assigned to each category. The third column lists the expected number of transmissions per sick person, for each category. The values are based on EpiSimS simulations which indicate that 50% of transmissions come from circulating symptomatic persons, 25% come from non-circulating symptomatic persons, and 25% come from persons with sub-clinical manifestations.

Table 4.3-1. Categorization of infected people in the source region, with expected transmissions per case there and in the US, with and without quarantine of symptomatic persons.

Fraction of source region cases	Category	Transmissions per case	US transmissions – no quarantine	US transmissions – quarantine of symptomatics
.333	Sub-clinical	$0.75 R_0$	$0.494 R_0$	$0.494 R_0$
.1055	Incubating will circulate	$1.5 R_0$	$1.5 R_0$	$1.5 R_0$
.1055	Incubating won't circulate	$0.75 R_0$	$0.75 R_0$	$0.75 R_0$
.228	Symptomatic circulating	$1.5 R_0$	$0.75 R_0$	0
.228	Symptomatic non-circulating	$0.75 R_0$	0	0
	Average	R_0	$0.573 R_0$	$0.402 R_0$

The fourth column gives the expected number of transmissions per infected traveler[3] that would occur in the US under the assumption that the travel time is distributed uniformly over the disease category. Persons in the symptomatic non-circulating category would not travel, so that category does not contribute to transmissions in the US. If a symptom-based quarantine program is applied, the transmissions from persons in the symptomatic circulating category can be eliminated, as shown in the last column.

An effective infectious arrival is defined such that one effective infectious arrival would transmit disease to R_0 persons upon arrival to the US. The number of effective infected arrivals per day is $0.573 * 1000 * f$ if no quarantine program is in place. If symptomatic persons are prevented entry, the effective number of infected persons arriving per day is reduced to $0.402 * 1000 * f$. 70% of the effective infectious arrival rate is due to non-symptomatic persons, and 30% is due to symptomatic persons.

At the computed epidemic growth rate of 7.2% per day in the source region, the epidemic in the US would be delayed by $\ln(.573/.402)/0.072 = 4.9$ days by a policy that prevents entry of all symptomatic persons, relative to a policy that does not restrict travel in any way.

For the planning scenario pandemics, in which 25%-40% of the population would be infected in the absence of national-scale vaccine or antiviral treatment programs, the arrival of as few as 10 infected persons would practically ensure an epidemic in the US. For unrestricted entry of international travelers, 10 infected persons will have arrived to the US by the time that the prevalence in the source

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[3] includes infected persons that travel from SE Asia to the US, or that would have traveled to the US but were incapacitated by illness.

region reaches 10 * 0.072 / 573 = 0.00125. If symptomatic persons are prevented from entering, 10 effective infected persons would have arrived to the US when the source region prevalence reaches 0.0018 (i.e. 5 days later). These levels of prevalence would be reached in the source region some 4 months after the transition to human-to-human transmission.

4.3.3 Quarantine Strategy 2: Travel Restriction

A second quarantine strategy would, in addition to preventing entry of all symptomatic persons, reduce the total number of travelers originating in regions in early epidemic stage. The strategy would account for 1) population of infected region, 2) fraction of population in infected region that normally enters the US each day, and 3) the epidemic prevalence. When the product of the above three factors reaches a triggering threshold, a travel restriction policy would be emplaced to reduce the number of travelers from the infected region with a multiplier of F. The triggering threshold might be 0.05 expected infected travelers per day, for the first infected region of a pandemic. Later in the pandemic, when there are many infected regions in the world, the threshold might be lowered to 0.01 (or less) expected infected travelers per day from a particular infected region.

The degree to which travel can be restricted will depend on many unknowns, so F is parameterized over the values {1.0, 0.5, 0.1, and 0.02}, i.e. {no restriction, reduction in half, ten-fold reduction, and fifty-fold reduction}. At these values, the respective effective arrival rates would be {402 f, 201 f, 40.2 f and 8.04 f} infected travelers per day, assuming symptomatic travelers are all prevented from entry. The respective delays in the US epidemic[4] would be {4.9 days, 14.5 days, 37 days, and 59 days}.

Quarantine Strategy 2 could provide a month or two of delay in the US epidemic if travel can be restricted by a factor of ten or fifty from infected regions during the early growth stage of their epidemic. This delay could prove invaluable in allowing time for development of effective vaccine.

As the prevalence in the infected region approaches its peak of 2.51%, even a 50-fold reduction in arrivals would give 0.2 effective index cases arriving to the US per day. In addition, some infected persons may travel through an intermediate third country, and face no restriction on their final leg. Quarantine Strategy 2 would thus be unlikely to prevent a US epidemic.

4.3.4 Quarantine Strategy 3: Reduce Travel within the US

A third quarantine strategy is to cut down on the number infected people arriving at a city or region from somewhere else in the US. A set of simulations based on Portland has been conducted to assess how long the epidemic can be delayed by using this regional quarantine strategy.

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[4] delay (days) = ln(arrival rate with no restriction / arrival rate with quarantine and restriction) / 0.072.

All persons are uninfected at the start of the simulation. The US epidemic is taken to have entered the early exponential growth stage when people begin to migrate into Portland. This inflow can be characterized by the maximum number of infected people entering Portland, which will happen at the peak of the infected city's epidemic. Experiments were conducted at maximum values of one, five, ten, and twenty infected people per day entering Portland. Figure 4.3-2 shows the number of infected people who arrive from out of town when the maximum is five people per day.

**Number of Arriving Infected People Per Day
5 Maximum**
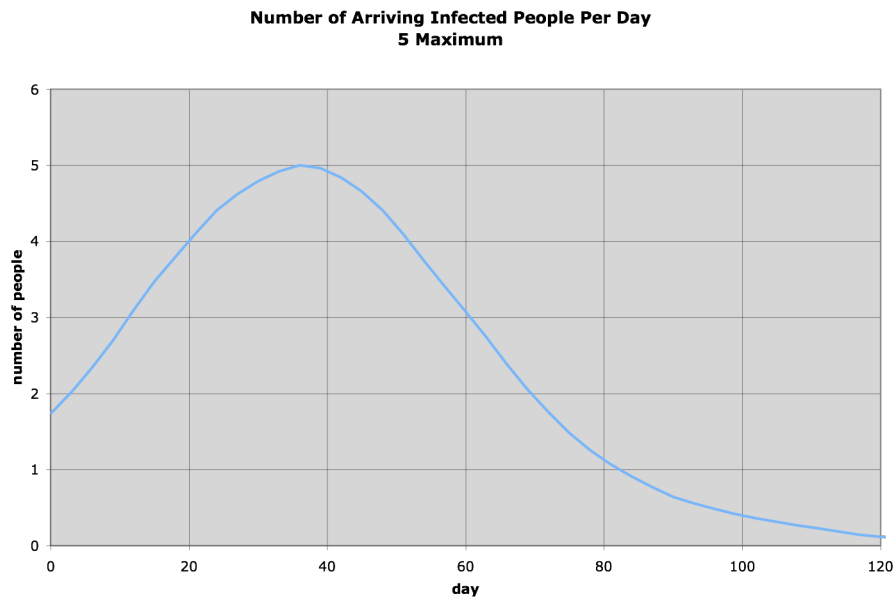
Figure 4.3-2. Number of infected people per day arriving in Portland.

An arriving person is added to our population by randomly choosing a person in our population to become newly infected. The EpiSimS simulations with arriving infected persons are compared to a base case run, in which 200 random people are infected simultaneously on day zero and no additional arrivals occur. Figure 4.3-3 shows an overlay of the epidemic curves (e.g. the number of new infections per day) of the base case simulation and a typical simulation result. For this run, the epidemic initiated by arriving infected persons is delayed 23 days relative to the base case simulation.

Comparison of 5 Infected Arrivals vs the Base Case
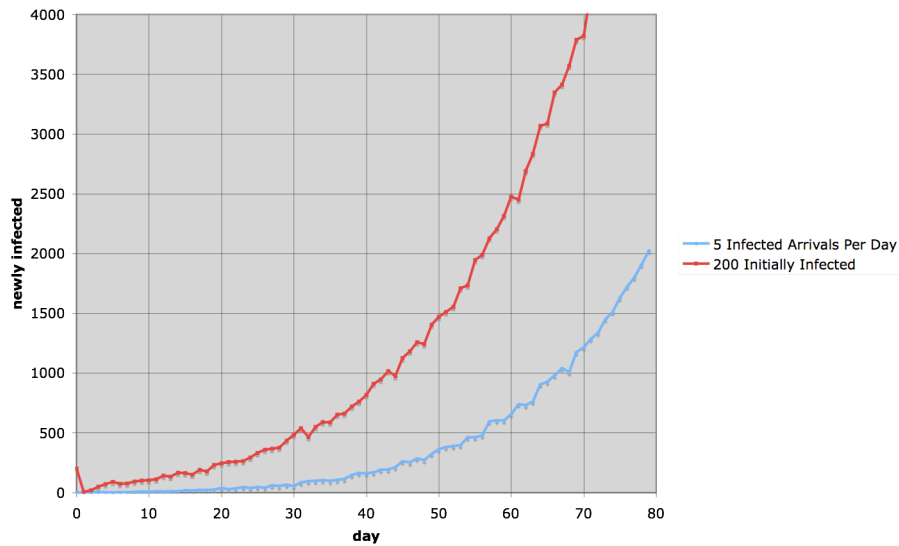
Figure 4.3-3 Comparison of a typical epidemic curve for epidemics initiated with arrivals of infected persons (peak of five infected arrivals per day) with the base case initiated by 200 simultaneous index cases.

In epidemics initiated with 200 infected persons, multiple simulations show little variation in the time at which the epidemic occurs (e.g. in the time at which 1000 or 5000 infections are attained). However, because of stochastic effects that occur when there are only a few or few dozen infected persons, there is a much larger variation in the epidemic timing when the epidemic is initiated gradually by arriving infected persons.

Figure 4.3-4 shows the delay in the epidemic due to a regional travel restriction strategy, for an ensemble of EpiSimS simulations conducted at several peak infected arrival rates. Cutting the influx of infected travelers from twenty per day to five per day will delay the onset of an epidemic by close to three weeks. Curtailing the infected travelers from ten per day to one per will give an additional 3 week delay.

**Delay of Epidemic
Via Curtailing Inter-city Travel**
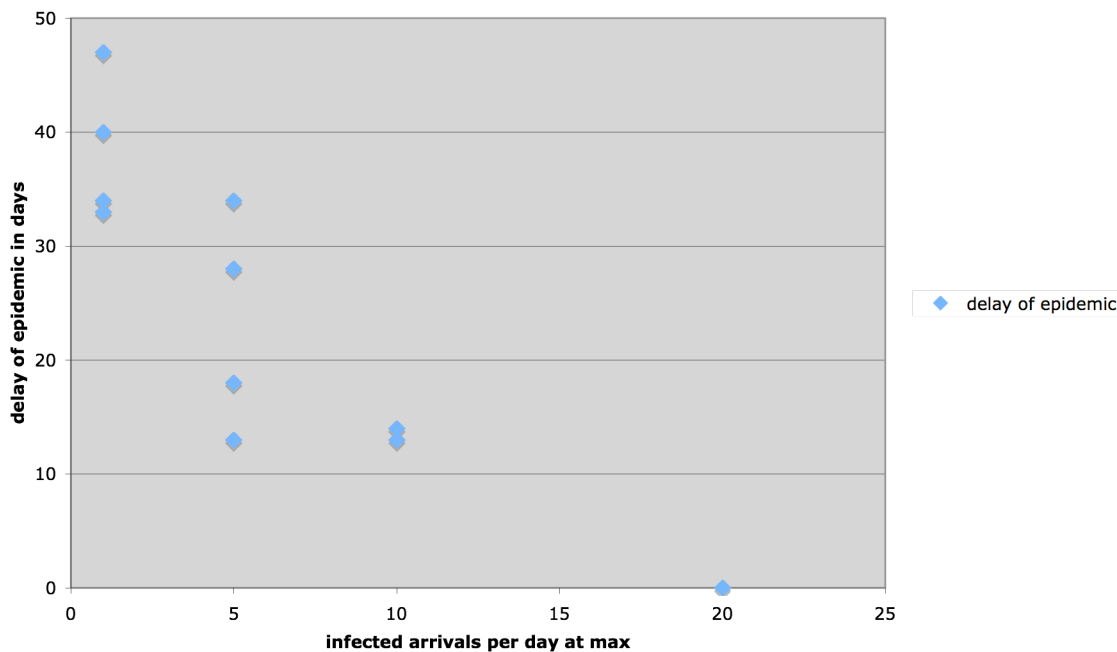
Figure 4.3-4 Delay in the epidemic in Portland attributable to reduction of the number of infected people that arrive from elsewhere in the US, computed with EpiSimS.

4.4 Analysis of Vaccination and Social Distancing Strategies Using Loki-Infection Model

4.4.1 Overview of Model and Results

Optimization of vaccination and social distancing strategies were assessed using a networked agent based model, Loki-Infection (NISAC) that incorporates social contact networks within a simulated community structure. The model community is designed to represent a typical community in the US comprised of 10,000 individuals. Results indicate that even using projected worst-case scenario model inputs that yield 50% infection rates (~5000 people) and 5% death rates (~500 people), there are opportunities for interventions that will at minimum delay and contain, and possibly even significantly reduce the effects of avian influenza at the scale of the community. Simulation results suggest that vaccination and social distancing strategies focused on children and teenagers can be very effective at reducing attack and death rates, particularly when vaccines are either unavailable or in limited supply. These strategies work because they target dense areas of the

social contact network along which influenza most easily spreads to the entire community.

Predicated on model assumptions, specific results include:

- A "children and teenagers first" vaccination strategy could be very effective in thwarting an influenza epidemic. All others within the community are protected by herd immunity rather than direct vaccination. Model results for the simulated community show that substantial reductions in infection and death rates could be achieved if the vaccine is administered and effective for ~60% of the children and teenagers.

- Similarly, social distancing of "children and teenagers only," could be highly effective in thwarting the spread of infection, especially in the absence of effective vaccines or antivirals. A social distancing policy would require those under 18 years of age to be restricted primarily to their homes for the duration of the epidemic. With this social distancing strategy, adults may continue to work and interact within the community as normal. If implemented quickly within the community (after 10 symptomatic individuals are discovered) and with full compliance, reductions in the number of people who are infected or die are above 97% for the simulated community. If compliance is relaxed to 70% so that children and teenagers maintain 30% of their normal social contacts outside the family, the number of people that are infected or die are still reduced by greater than 84%.

4.4.2 Model Description and Base Case Results with No Mitigation

Loki-Infection, introduced here, is one of a suite of networked agent-based models developed by NISAC to analyze complex adaptive infrastructures. Loki-Infection models the spread of an infectious disease within a complex social network. This network incorporates a realistic community structure of individual-to-individual contacts within multiply-overlapping groups, as may be built from demographics, expert elicitation or behavioral surveys where available. For the current set of analyses, a representative US community of 10,000 was simulated. It is composed of four age classes (children, teenagers, adults, and seniors), and is structured into typical social groups such as families, school classes, businesses, and senior gatherings. Within and across groups, social links are created with given frequencies of contact along which the disease can spread.

The transfer of influenza through individual contacts within the social contact network is represented as a stochastic process dependent on the frequency of contact as well as each individual's infectivity and susceptibility, with infectivity a function of the progression of the illness (e.g., latent, infectious pre-symptomatic, infectious symptomatic, infectious non-symptomatic). Parameter values used for the natural history of a highly pathogenic influenza strain were

comparable to those reported in two recently published modeling studies[5, 6]. To consider a severe pandemic, parameters for the overall disease infectivity and mortality were set to yield influenza total infectious attack rates of ~50% (percentage of a community that will have influenza, approximately half of which will develop clinical symptoms) and death rates of ~5% of the total population.

Base Case, No Mitigation Strategies employed: Simulated community of 10,000 suffers an average of 5,064 infected individuals (attack rate[7] of ~51%), out of which ~465 die (death rate[8] of ~4.7%). The average outbreak peaks at 44 days and lasts 113 days. Analysis of results yields an average reproductive number, R_0, for comparison to classical SIR models of ~1.8 and an average time between generations of 3.1 days.

Analysis of this base case shows the critical importance of children and teenagers in the spread of influenza. Their importance comes from three characteristics. First, on average, children and teenagers each have 50% more contacts per day than adults. Second, the social contact network construes most of the contacts for children and teenagers to be like-to-like with nearly half taking place in school or day-care centers. Third, children and teenagers are often both more infectious and more susceptible than adults. From sensitivity studies, it is found that the first two of these are of most important.

4.4.3 Vaccination Scenarios

Loki-Infection was used to investigate vaccination strategies assuming that an effective[9] vaccine is produced, but quantities are limited. As mentioned above, model results are predicated on a description of a representative social contact network within a generic US community of 10,000 individuals. Model results are as follows:

Unlimited Vaccine Available:

Without vaccine shortages, assuming current (typical) vaccination rates in the US (26% of children aged 0-10, 26% of teenagers aged 11-18, 30% of adults aged 19-65, 59% of seniors aged > 65) as well as 100% vaccine effectiveness, attack and

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[5] Ferguson, N.M., et al., *Strategies for containing an emerging influenza pandemic in Southeast Asia.* Nature, 2005. 437(7056): p. 209.

[6] Longini, I.M., et al., *Containing pandemic influenza with antiviral agents.* American Journal of Epidemiology, 2004. **159**(7): p. 623

[7] Attack rate is defined as ratio of the total number of people who become infected to the total number of people in the community expressed as a percentage. In our model, half of the people who become infected develop symptoms.

[8] Death rate is defined as the ratio of the total number of people who die to the total number of people in the community expressed as a percentage

[9] Within the scenario runs, vaccine effectiveness was assumed at 100% for those vaccinated.

death rates in the model community are decreased by 65% and 69% from the base case, respectively.

Vaccine Shortage:

Vaccinate Senior Citizens (ages > 65): A strategy of vaccinating only and all seniors, who have an assumed mortality rate 5 times higher than those of other age classes in the model, was considered. With this strategy, the death rate was decreased by 24% (compared with the base case) and the attack rate by only 4%.

Vaccinate Children and Teenagers (ages < 19): Based on the critical importance of children and teenagers in the spreading of influenza found in the base case simulations, a strategy of vaccinating only these groups was considered. Such a strategy is found to be very effective with essentially complete suppression of influenza within the community if ~60% of the children and teenagers are vaccinated. This "children and teenagers first" vaccination policy protects the entire population and requires only ~17% of the total population to be vaccinated, 50% less than the only partially effective current policy. Results are shown as red squares in Figure 4.4-1, below.
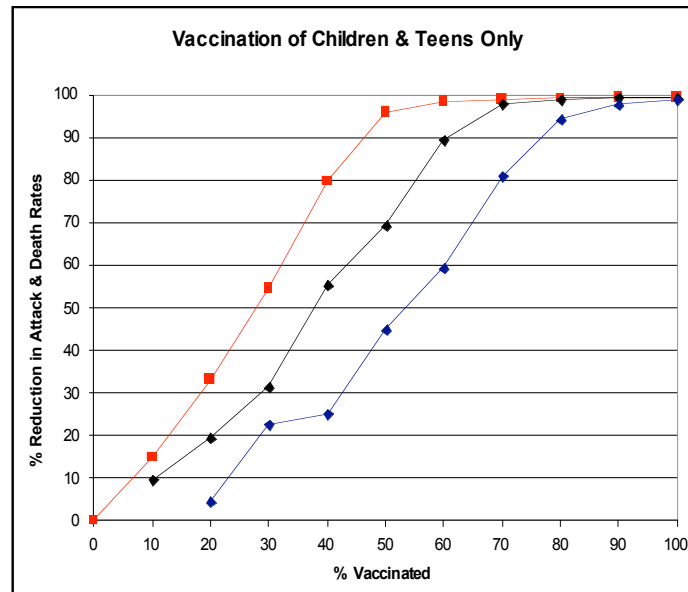
Figure 4.4-1. Reduction in infections and deaths relative to base case simulations for vaccination strategies that focus only on children and teenagers only. Red squares represent influenza infectivity as currently expected for a pandemic strain ($R_0 \sim 1.8$). Nesting curves that lie below are for increasingly virulent strains with higher values of R_0 (2.25 and 2.7).

4.4.4 Social Distancing

Loki-Infection was used to examine the effects of social distancing applied preemptively and structurally so as to reconfigure the contact network within the community. Based on the significant influence of children and teenagers on the spread of influenza noted above, preemptive social distancing of these age groups was examined.

A preemptive social distancing of children/teenagers is implemented in the model when the number of symptomatic individuals within the community reaches a given threshold, i.e., the policy implementation threshold. Once implemented, schools are closed and children and teenagers are sent home where they remain until all symptoms of the flu have left the community. All adults (and seniors) continue to go about their day-to-day routines except that they avoid contacts with children/teenagers who are not their own. On average, 30 contacts per day per child/teenager are influenced (80% in the classroom setting alone).

The reduction in attack and death rates as a function of the policy implementation threshold is shown in Figure 4.4-2, below. If this strategy were to be implemented after only 10 symptomatic individuals were detected, there would be no further influenza outbreaks in the local community, with reductions of over 97% in the number of infected and dead relative to the base case (no social distancing or vaccination). If preemptive structural quarantine (social distancing) is not imposed until 80 individuals (0.8% of population) are detected (possibly a worse case), attack and death rates would still be reduced by ~87% relative to the base case. Additional simulations show that little is gained by preemptively social distancing of additional groups (other than children/teenagers).

Preemptive Structural Social Distancing of Children & Teens
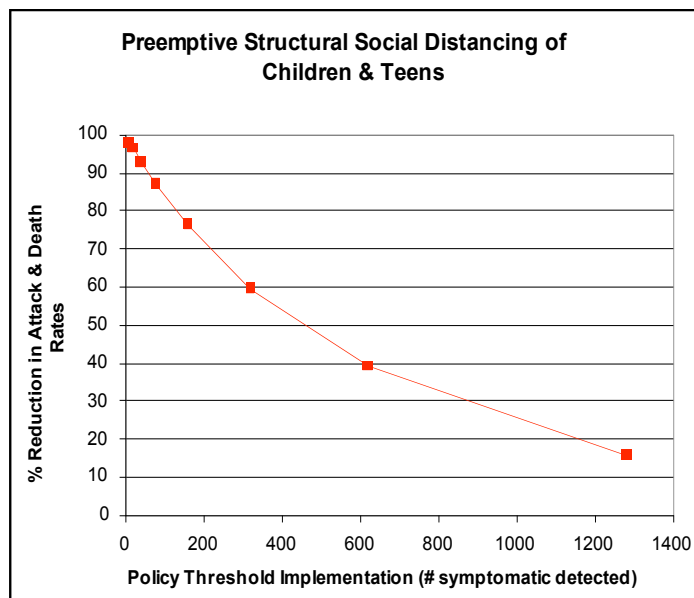
Figure 4.4-2. Reduction in infections and deaths relative to base case simulations for social distancing strategies that focus only on children and teenagers. The strategy of closing schools and sending children and teenagers home where they remain for the duration of the epidemic is implemented after varying numbers of symptomatic people are detected within the community (red squares). The more quickly the strategy is implemented the more successful, but it is still quite effective after even 80 (0.8% of population) symptomatic are found.

It is recognized that not every child and teenager (or parent enforcer) will follow a policy directive for social distancing. Additional simulations, shown in Figure 4.4-3 for a policy threshold of 10 symptomatic individuals, suggest that 80% compliance may still result in attack and death rate reductions of greater than 94%. Further relaxation to 70% compliance, still reduces influenza severity within the community by above 84%.

While these results are compelling, a drawback of social distancing strategies is that they must be imposed for at least the duration of the local epidemic, and possibly for the entire period of the pandemic if infected individuals are permitted to enter the community.
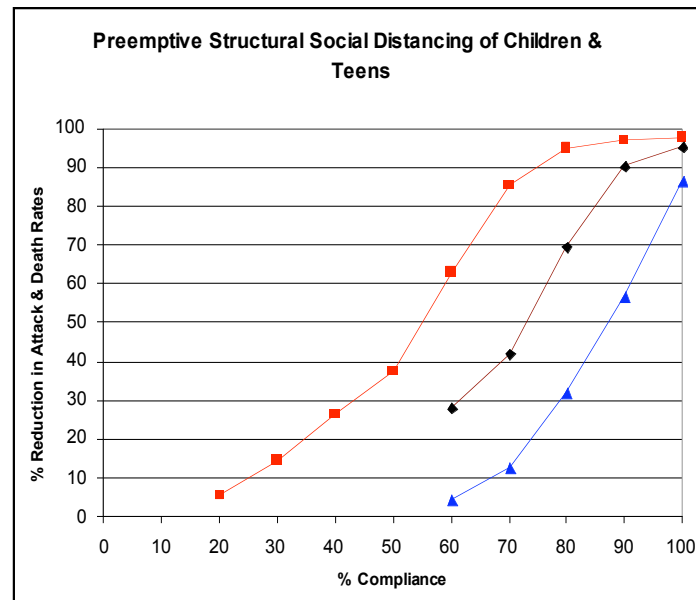
Figure 4.4-3. Reduction in infections and deaths relative to base case simulations for social distancing strategies that focus only on children and teenagers. If we assume that compliance will not be full, we still find that if 70% of the normal contacts for children and teenagers are distanced, then the strategy is effective to above 85% (red squares). Curves below the red squares are for more virulent strains of influenza.

4.4.5 Robustness of Results for Vaccination and Social Distancing Strategies

The robustness of results reported above for both vaccination and social distancing were probed in two ways. First, the assumed increased infectivity and susceptibility of children and teenagers was removed as this may not be the case for the influenza strain that erupts. Such removal did not change results. Second, the disease infectivity was increased by 25% and 50% to consider much more virulent strains (note that increasing to 50% yields an R_0 if 2.7, far beyond any influenza that has been recorded). Results were plotted as the nested set of curves lying below the red squares in previous figures. Increasing influenza infectivity does decrease the effectiveness of the both the "children and teenagers first" vaccination and social distancing strategies and thus requires higher vaccination or compliance for the same benefit. The effectiveness of vaccinating children and teenagers has also been advocated by Longini and coworkers[10, 11, 12] from results

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[10] Patel, R., I. M. Longini, et al. (2005). "Finding optimal vaccination strategies for pandemic influenza using genetic algorithms." Journal of Theoretical Biology **234**(2): 201.

[11] Halloran, M. E., I. A. Longini, et al. (2002). "Community interventions and the epidemic prevention potential." Vaccine **20**(27-28): 3254.

[12] Weycker, D., J. Edelsberg, et al. (2005). "Population-wide benefits of routine vaccination of children against influenza." Vaccine **23**(10): 1284.

obtained using a different modeling approach. The overlap of their results with our results gives greater weight to the likely effectiveness of this strategy.

4.5 Comparative Analysis of Antiviral Strategies Using Avian Influenza Discrete Event Simulation Model

4.5.1 Model and Application

The avian influenza discrete event model uses Monte Carlo simulation to investigate the propagation of influenza through a population. This model was used to examine three distribution strategies for the prophylactic use of antiviral medications, as follows:

1. Mass prophylaxis. Antiviral drugs are randomly provided to varying percentages of the population. It is assumed that that there is no time delay in antiviral distribution.
2. Contact tracing prophylaxis: Antiviral drugs are provided to the possible contacts (previous, current, and future) of an infected person. The accuracy of the contact lists and the success rate for getting the antiviral to the contact on time are varied.
3. Targeted prophylaxis: Antiviral drugs are provided to children and teenagers only.

The disease process stages[13] are illustrated in Figure 4.5-1 below and described as follows:

- Stage 1: Exposed and pre-symptomatic stage: duration of the stage is triangularly distributed across 1 to 2 days, centered over a duration of 1.5 days. The probability of transmission (chance of disease spread by an infective) is 0.5.

- Stage 2.1: Symptomatic stage: duration of the stage is triangularly distributed across 1 to 3 days, centered over a duration of 3 days. The probability of transmission (chance of disease spread by an infective) is 0.5.

- Stage 2.2: Asymptomatic stage: duration of the stage is exponentially distributed with a mean of 3 days. The probability of transmission = 0.5.

- Stage 3: Hospitalized stage: duration of the stage is uniformly distributed across 1 to 14 days, and has a probability of transmission = 0.05.

- Stage 4.1: Dead

- Stage 4.2: Recovered

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[13] Source: Joseph Wu, S. Riley, G. Reung, and C. Fraser, Pandemic Flu: Catch Me if You Can, *INFORMS Annual Conference*, Nov. 2005.

CIP/DSS

Susceptible → Expos.& Pre-Sym. → Sympt. (68%) → Hospitalized (6%) → Dead (17%)

Expos.& Pre-Sym. → Asymptomatic (32%)

Sympt. → Recovered (94%)

Hospitalized → Recovered (83%)

Asymptomatic → Recovered
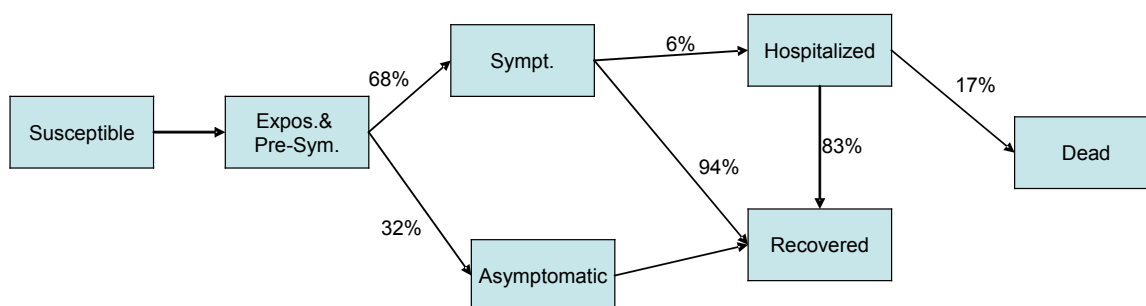
Figure 4.5-1. Stages in the Propagation of Avian Influenza using the Discrete Event Model

The characteristics of the model community are:

- The entire population is composed of 29% children and teenagers, and 71% adults.

- Twelve people are initially randomly infected with avian influenza

- Each infective (infected person) passes through stages as shown in the figure above, and produces secondary cases in one of stages.

- For production of secondary cases by an infective, an infective connects with a number of contacts. Some of these are randomly selected as new infectives to comply with the R_0 value, the ratio of newly infected per existing infected persons. Values of R_0 and contact demographics are given for the two population age groups in Table 4.5-1 below

Table 4.5-1. R_0 and Contact Demographics for the Two Population Age Groups in the Model Community

Ages	R_0	Average Number of Contacts	Contact demographics
Children and Teenagers	1.8	10	80 % Children and Teenagers 20% Adults
Adults	1.8	5	40% Children and Teenagers 60% Adults

For this study, antiviral intervention proceeds as follows:

Joint NISAC – CIP/DSS AI Analyses for Exercise Support   Page 44

- After seven people are diagnosed as infective, the regional government starts an intervention policy.

- It is assumed that antiviral drugs are available for a limited percentage of the total population.

- The antiviral drugs are administered according to the three strategies given above: Mass prophylaxis (randomly provide to a percentage of the population), prophylaxis to contacts, prophylaxis to some percentage of children and teenagers.

- In all cases, it is assumed that there is no delay for the antiviral distribution to the population.

- Antiviral efficacy parameters: It is assumed that antivirals are only effective for these two areas:
  - 70 % reduction in susceptibility by the use of antiviral (Reduction of susceptibility = 0.7)
  - 31 % reduction in infectivity by the use of antiviral (Reduction of infectivity = 0.3)

4.5.2 Model Results for Mass Antiviral Intervention Policy

The percentages of population receiving antivirals were varied to investigate the amount of antiviral required to reduce the number of infective persons and finally eradicate the pandemic. The results of the simulation (see Figures 4.5-2 through 4.5-5 below) show, as expected, that if a sufficient percentage of the population is provided with antivirals, the transmission rate can be slowed and the pandemic can be eradicated. The figures all show the number of infectives (individuals infected) as a function of time if different population percentages are supplied with antivirals.

For the model community, the figures below show that transmission rates slow when 55% of the population are given antivirals, and the pandemic is eradicated when that number is increased to 60% or above. The model results indicate that there is a break point, or tipping point, for containing the illness. Once more is known about a disease outbreak and parameters, this simulation can be run with more accurate assumptions to provide a closer estimation of the true tipping point.
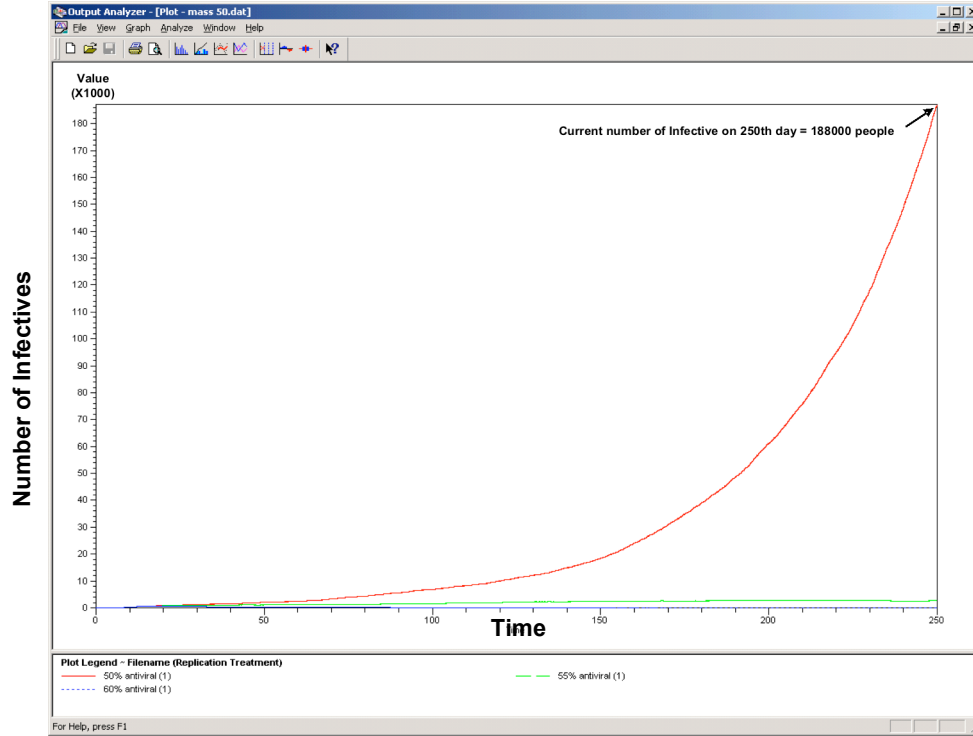
Figure 4.5-2. Number of Infective Persons vs. Time for Antiviral Distributions to 50% (red), 55% (green), and 60% (blue) of the General Population. Y-axis scale is 0 to 180,000; X-axis scale is 0 to 250 days.

Figure 4.5-3. Number of Infective Persons vs. Time for Antiviral Distributions to 55% (red), 60% (green), 65% (blue), and 70% (black) of the General Population. Y-axis scale is 0 to 3,500; X-axis scale is 0 to 250 days.
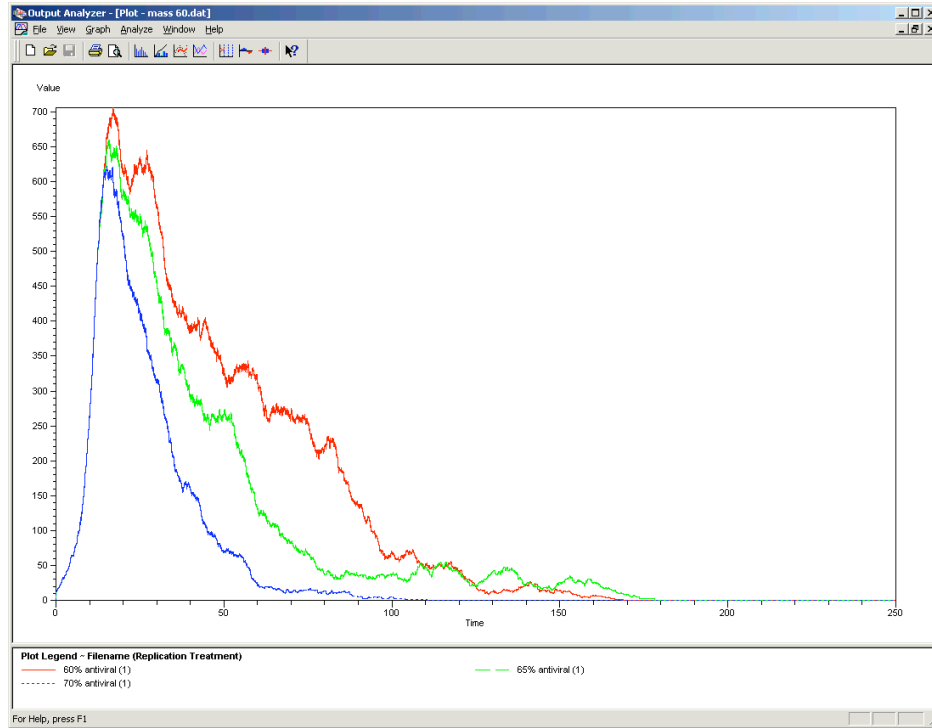
Figure 4.5-4. Number of Infective Persons vs. Time for Antiviral Distributions to 60% (red), 65% (green), and 70% (blue) of the General Population. Y-axis scale is 0 to 700; X-axis scale is 0 to 250 days.
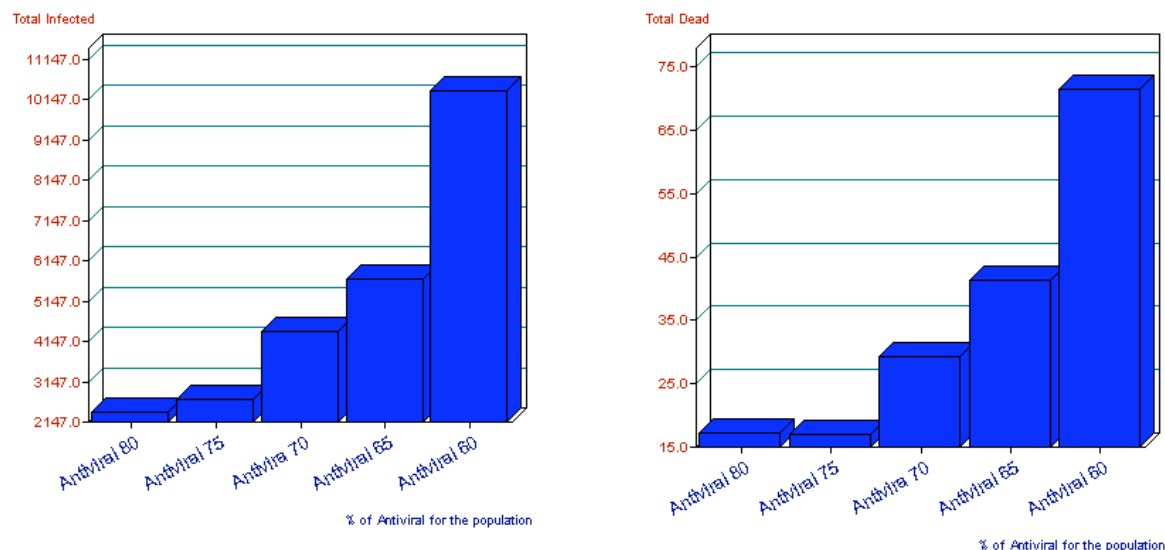
Figure 4.5-5. Total Numbers of Infective and Dead for Various Percentages of Antivirals Distributed to the General Population.

4.5.3 Model Results for Contact Tracing Antiviral Intervention Policy

A suite of model runs were conducted to investigate the accuracy with which contacts (previous, current, and future) would need to be ascertained, and the success that would be required for distribution of antivirals within the necessary amount of time. The percentages of both *Accuracy of Tracing* and *Success of Tracing (on time)* were varied to investigate the values of these variables required to reduce the number of infective and finally eradicate the pandemic. The simulation results are shown in the two figures below. In order to reduce the number of infective and halt the pandemic, *Accuracy of Tracing*, multiplied by *Success of Tracing (on time)* must be greater than 0.45 for the model community. For example, if *Accuracy of Tracing* is 60 %, *Success of Tracing* must be greater than 75%. Therefore, the success of the contact tracing policy depends upon accurate identification of possible infective contacts, and the speed with which antivirals can be distributed.
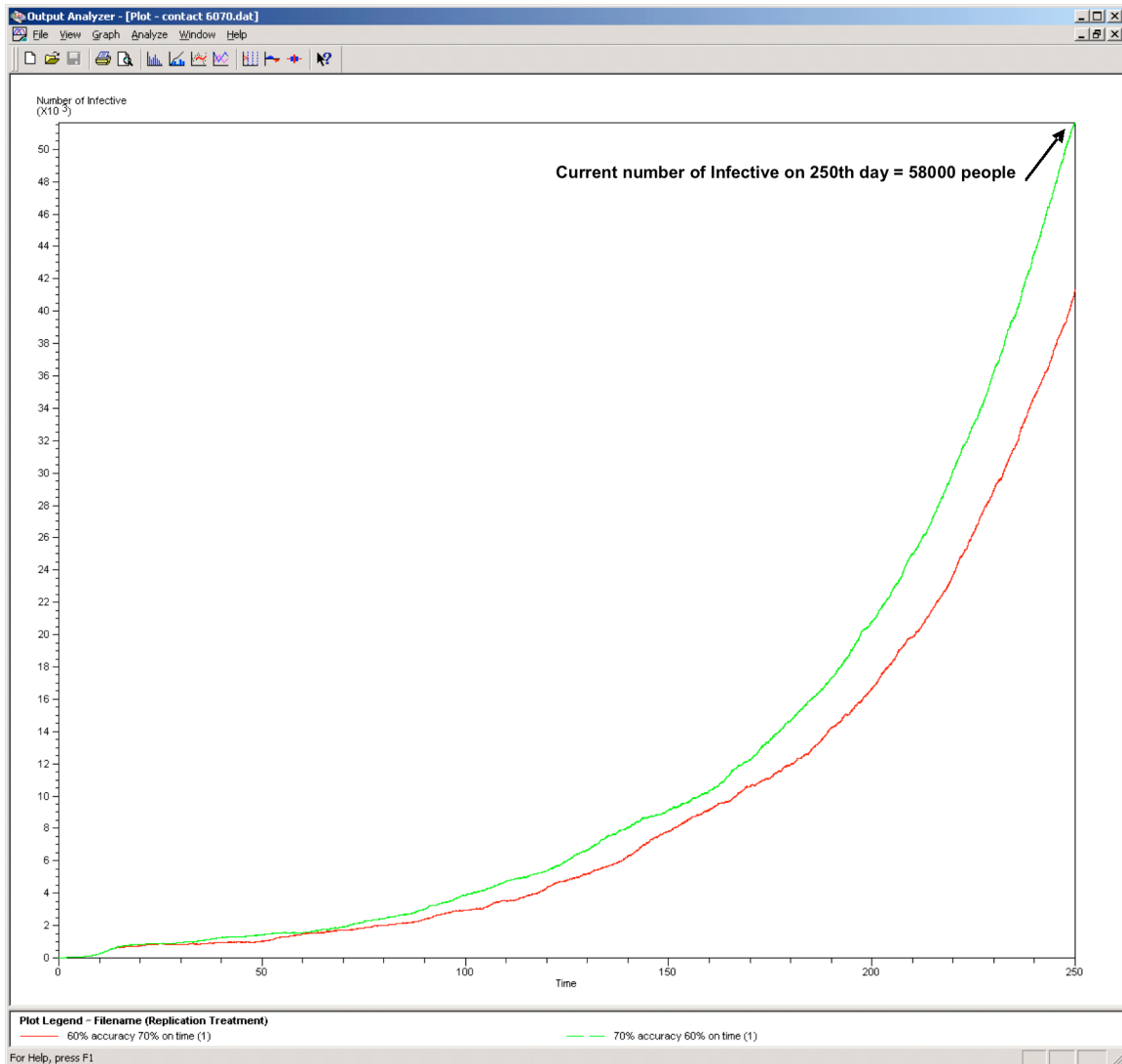
Figure 4.5-6. Number of Infective Persons vs. Time for Contact Tracing Parameters of
60% Accuracy of Tracing and 70% Success of Tracing (red), and 70% Accuracy of
Tracing and 60% Success of Tracing (green).
Y-axis scale is 0 to ~51,000; X-axis scale is 0 to 250 days.
These two curves are different only because of random differences introduced by the
Monte-Carlo method. They could equivalently be reversed.
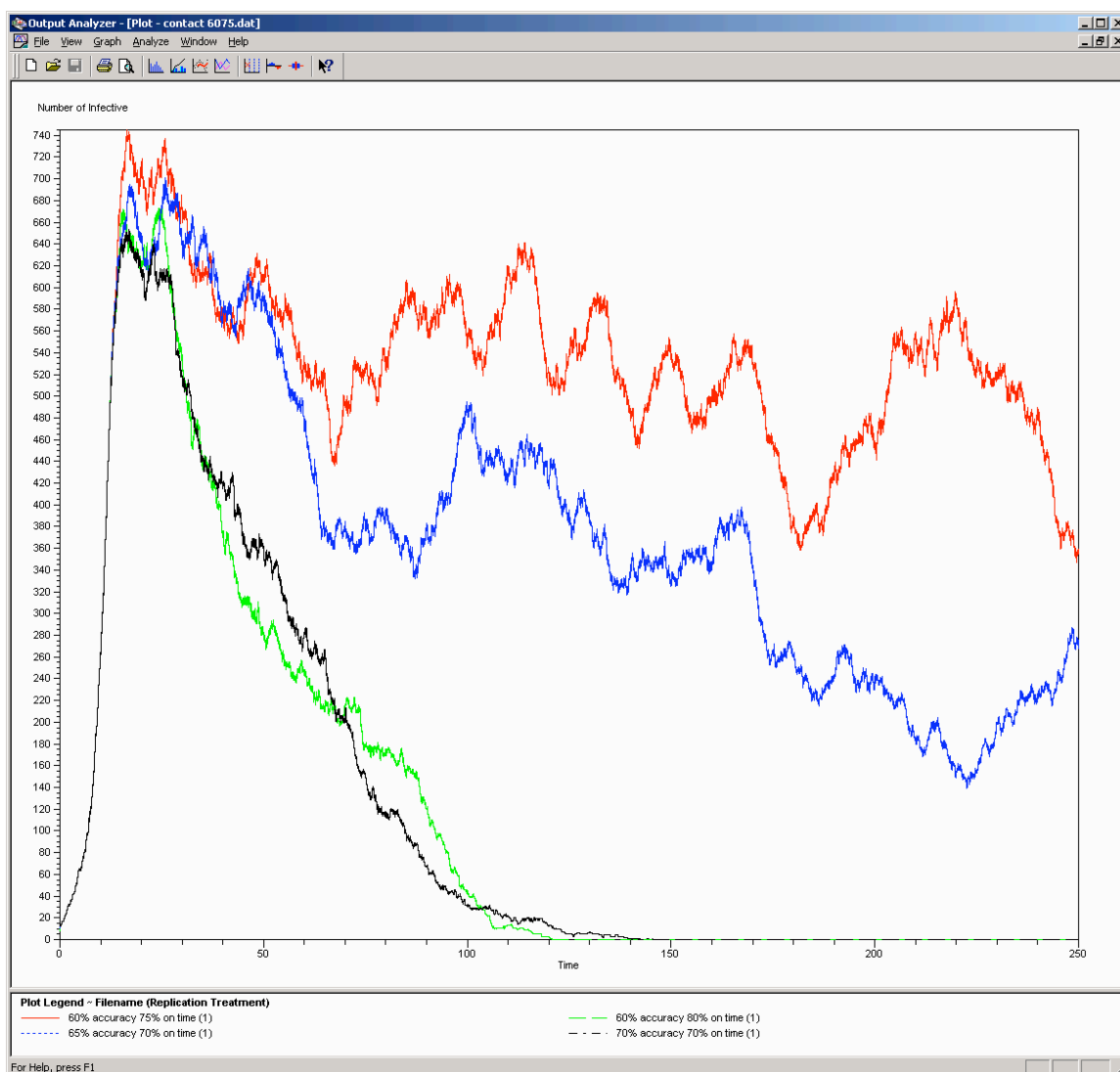
Figure 4.5-7. Number of Infective Persons vs. Time for Contact Tracing Parameters of 60% Accuracy of Tracing and 75% Success of Tracing (red), 65% Accuracy of Tracing and 70% Success of Tracing (blue), 60% Accuracy of Tracing and 80% Success of Tracing (green), and 70% Accuracy of Tracing and 70% Success of Tracing (black). Y-Axis scale is 0 to 740; X-axis scale is 0 to 250 days.

4.5.4 Model Results for Antiviral Intervention for Children and Teenagers Only

A set of model runs were conducted to investigate the impacts of providing antivirals to only children and teenagers. It was assumed that 100% of children and teenagers receive antivirals when the initial 7 symptomatic individuals are

hospitalized. It was further assumed that antivirals either continue to be administered or retain their efficacy through the duration of the pandemic. In order to evaluate this targeted policy, the average number of secondary cases generated by a primary case (R_0 value) associated with children and teenagers (R_{0c}) and adults (R_{0a}), were varied, while the average R_0 for the community was maintained at 1.8. Model runs were then used to investigate pandemic progress with various combinations of R_{0c} and R_{0a}.

Simulation results are shown in Figures 4.5-8 and 4.5-9, below. Figure 4.5-8 shows that for the default condition (both R_{0c} and R_{0a} equal to 1.8), and for a slight variation (R_{0c} of 2.0 and R_{0a} of 1.6), this policy cannot halt the pandemic.

Figure 4.5-9 shows that if adults are less infective ($R_0 < 1.4$), this policy can stop the pandemic. As would be expected, for a 100% effective antiviral policy in children and teenagers, the smaller the R_0 of adults, the sooner the pandemic is halted.
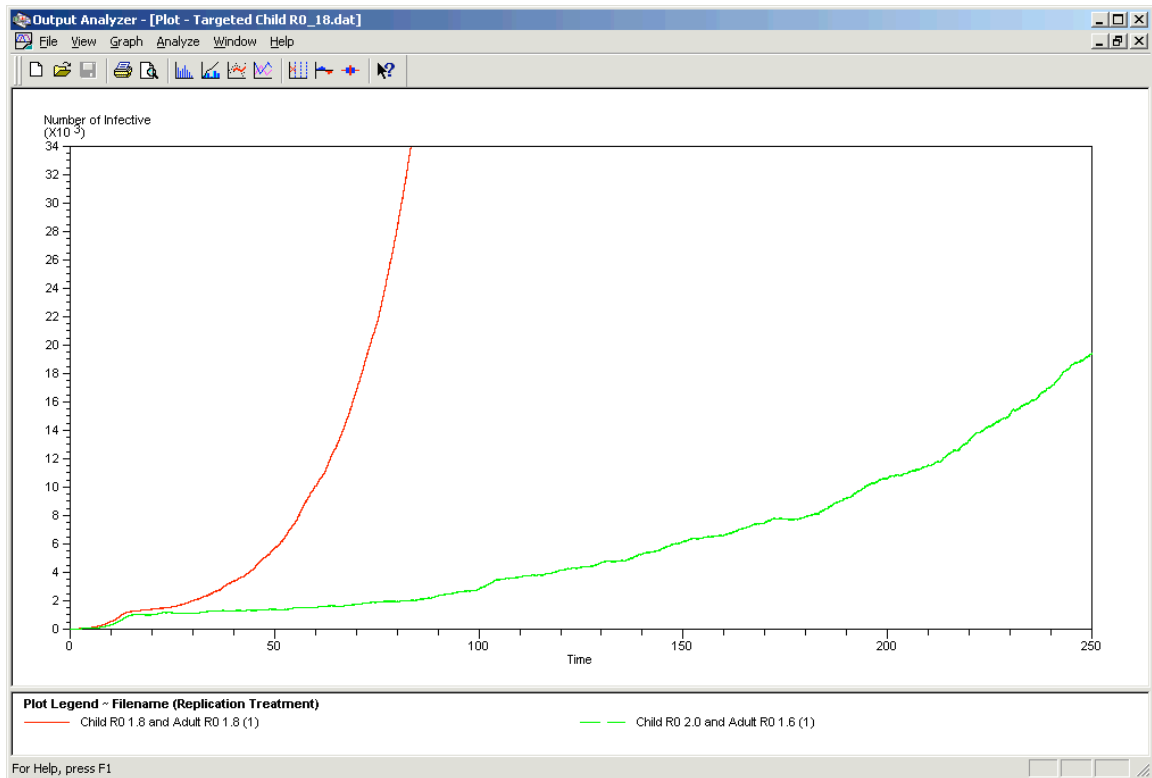
Figure 4.5-8. Number of Infected Individuals as a Function of Time for Combinations of $(R_{0c}, R_{0a}) = (1.8, 1.8)$, red line, and (2.0, 1.6), green line.
The Y-Axis scale is 0 to 34,000; X-axis scale is 0 to 250 days.
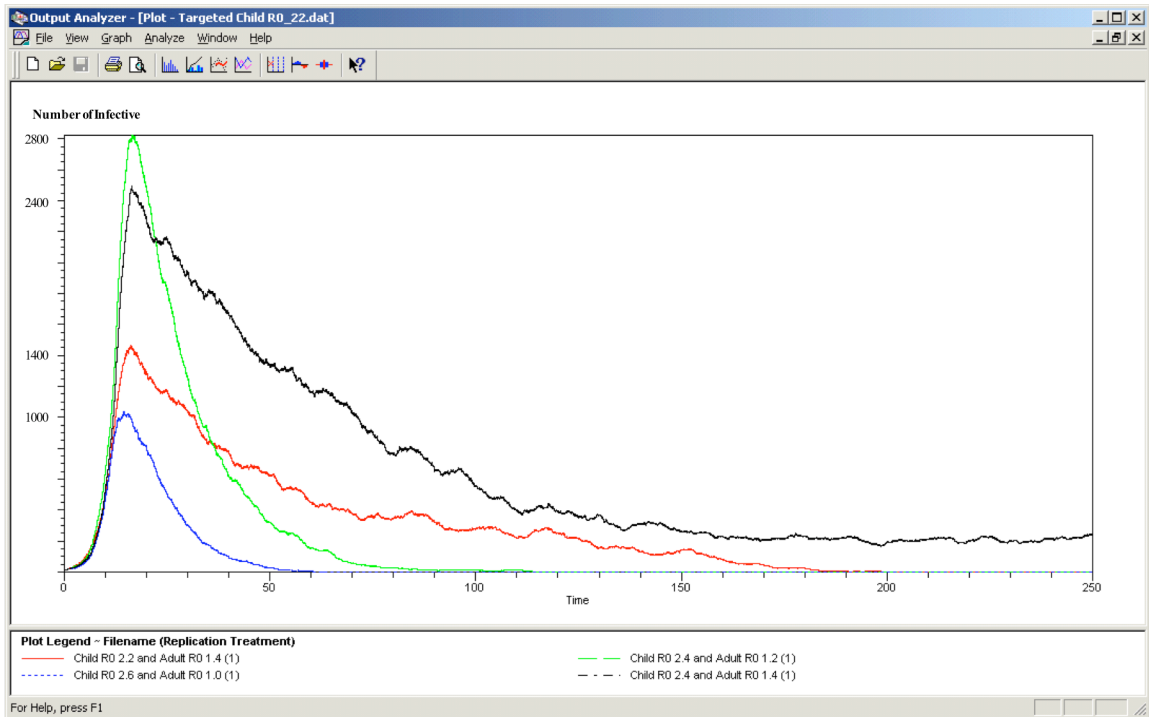
Figure 4.5-9. Number of Infected Individuals as a Function of Time for Combinations of $(R_{0c}, R_{0a}) = (2.2, 1.4)$, red line, $(2.4, 1.2)$, green line, $(2.6, 1.0)$, blue line, and $(2.4, 1.4)$, black line.

4.6 Analysis of Partially-Effective, Late-Arriving Vaccine Using EpiSimS

4.6.1 Implementation of model for vaccines and antivirals

This section describes a quantitative analysis of the dynamics of an epidemic with partially effective vaccine becoming available part-way into the epidemic. A new series of simulation experiments was conducted with the simulation tool EpiSimS, to compare the effectiveness of different vaccine effectiveness, and different dates of availability of the vaccine.

The study was conducted by simulating influenza epidemics within the city of Portland, Oregon. Publicly available data were used to generate 180,000 specific locations where social contacts occur: households, schools, colleges, workplaces, shopping centers, and social recreational areas. A synthetic population of 1,615,860 residents was used based on the 2000 US census data with demographics closely matching the real population. Realistic daily activities for each person were assigned based on activity surveys. The simulated movement of this population was analyzed over the course of an epidemic.

The influenza model consists of four main epidemiological stages: susceptible, incubating, infectious, and removed. All persons in the population are initially susceptible. The sojourn-time distributions of both the incubation stage and the infectious stage were implemented as half-day resolution histograms, based on historical data of the influenza pandemics of 1918, 1957, and 1968. The mean incubation stage duration is 1.9 days, and the mean infectious stage duration is 4.1 days. The infectious class is sub-divided into three categories: sub-clinical infectious (33.33% of the cases), symptomatic non-circulating (33.335%), and symptomatic circulating (33.335%). A person exiting the infectious stage is removed either through recovery or death. The case-fatality rate is taken to be 2% independent of age, based on the 1918 influenza pandemic. Upon entering an infectious stage, people modify their behavior: demographic-dependent fractions of such persons cease their normal activity patterns.

4.6.2 Base-case Scenario: No Effective Vaccine or Antiviral Treatments

For the planning scenario in which 25 to 40% of the population would become infected during the epidemic, we have confirmed that once ten individuals have been infected, an epidemic is virtually ensured, in the absence of a mitigating response. Even so, during the early growth of the outbreak (i.e. until ~200 cases have occurred), there are stochastic effects that generate variance in the timing of the epidemic. However, after reaching the level of about 200 infections, further variance is relatively small, and the courses of an ensemble of epidemics can be represented by a single high-fidelity simulation. The baseline EpiSimS simulation is initiated at this point in the outbreak by starting with 202 initial cases on simulation day zero. After a period of equilibration, the generations overlap into a continuum of disease stages, and the epidemic undergoes a phase of exponential growth. The growth rate drops as susceptible persons are removed. The baseline epidemic attains a peak new infection rate 98 days after the initial infections, and lasts 283 days (to the removal of the last infectious person). For the base-case scenario 420,274 people are infected (26% of the population) and 5,611 people die (Table 4.6-1).

4.6.3 Impact of Partially-effective Vaccine for 40% of the Population

The vaccine used against normal epidemic influenza is taken as the benchmark for nominal effectiveness. This vaccine produces immunity in 70% of treated individuals. In addition, in the 30% of vaccinated individuals that remain susceptible to infection, the course of the infectious period is shortened by an average of one day, and the infectiousness during the infectious stage is reduced by 80%. A partially-effective vaccine is taken to be half as effective as this nominal benchmark effectiveness. Thus the partially effective vaccine would produce immunity in 35% of treated individuals, reduce the average infectious period by 0.5 days, and reduce the infectiousness during the infectious stage by 40%.

Currently, manufacturers need an estimated 6 to 9 months to develop a flu vaccine. The new avian-related influenza virus could spread throughout the world before large-scale manufacturing can be initiated. Therefore, for both scenarios, we considered the effect of starting vaccinations at day 0 (at the beginning of the epidemic), 70 (at the rise), 98 (at the peak), and 127 (at the fall). We used optimistic delays because it is possible that during a flu pandemic, vaccine manufactures will be able to develop vaccines at a faster rate due to government policy.

The first intervention in Table 4.6-1 (also shown in Figure 4.6-1) corresponds to different starting days for a partially effective vaccine. This strategy is the most effective if implemented early (2,852 cases and 29 deaths if distributed at day 0). However, delaying the start of such an intervention to day 127 results in 394,233 cases and 5,185 deaths. We obtained similar results assuming a 70% effective vaccine (Table 4.6-1 & Figure 4.6-1). Figure 4.6-1 shows the daily number of cases of influenza for both levels of vaccine efficacy. The graphs demonstrate that both levels would have similar effects in the overall impact of the influenza pandemic. Therefore, in order for partially effective vaccines to benefit the population as a whole, they must be distributed early. Early identification of influenza cases and timely vaccine manufacturing is crucial in limiting the size and length of an outbreak.
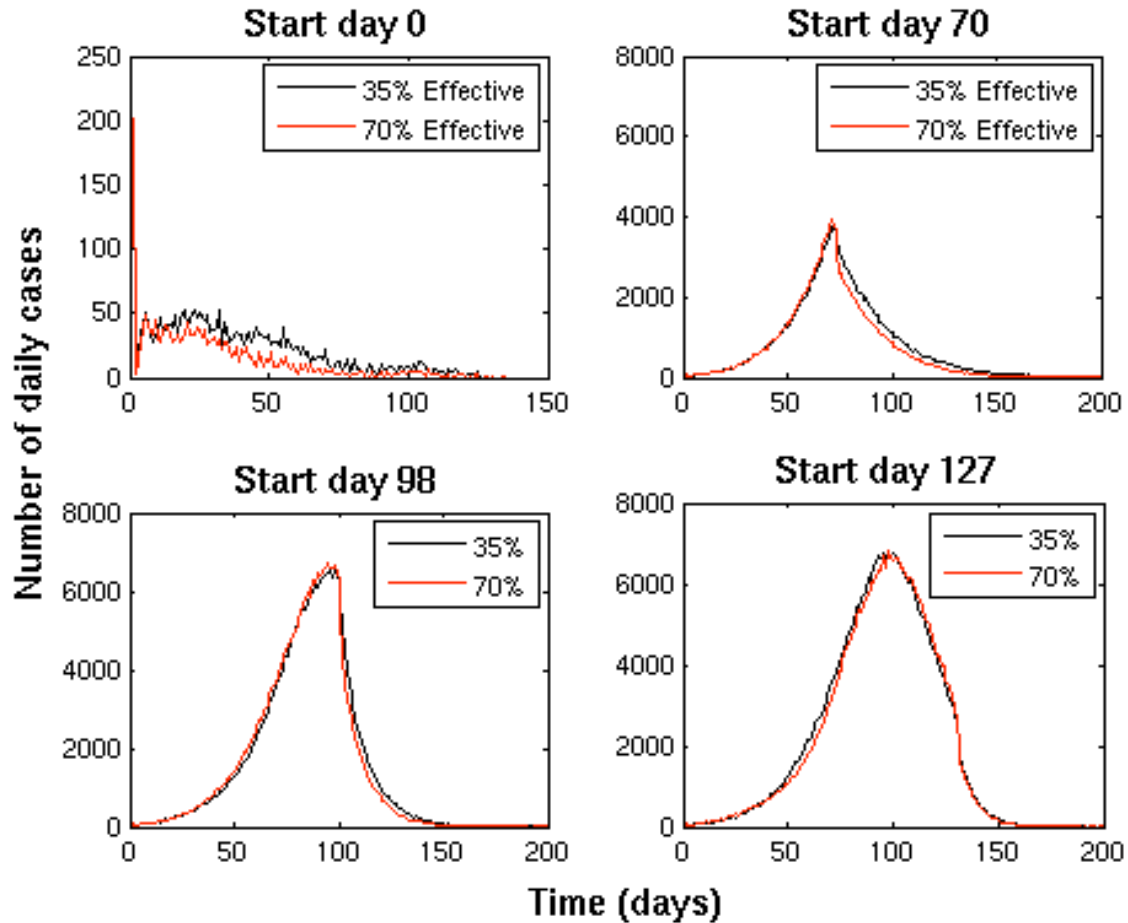
Figure 4.6-1. New influenza infections per day, with mass vaccination of randomly-selected 40% of the population, at four different start days with two levels of vaccine efficacy.

4.6.4 Impact of Partially-effective Vaccine for 20% of the Population

The risks of complications, hospitalizations, and deaths from influenza are higher among children, elderly persons, and persons with underlying medical conditions. To reduce the risk of hospitalization from complications of influenza, the Center for Disease Control (CDC) recommends routine annual vaccination of children and elderly. Thus, in our simulations under the targeted vaccination strategy, individuals under the age of 18 and over the age of 65 are vaccinated. The percentage of people in these categories is 38% of the entire population (27% children, 11% elderly). However, due to lack of a pandemic flu vaccine and delays in vaccine manufacturing, we assume that limited amount of vaccine enough to cover 52% of these populations (20% of the whole population), is distributed at four different stating days, 0, 70, 98, and 127. Furthermore, we considered two levels of vaccine efficacy: 35% and 70%.

Vaccination of 52% percent of children and elderly reduces the number of cases, if distributed early. Nevertheless, the results show that if the vaccine is distributed on day 0, the epidemic is extended for both levels of vaccine efficacy. If targeted vaccination is implemented on day 70, the total number of cases with a 35% and 70% effective vaccine would be approximately 211,319 and 197,151, respectively (Table 4.6-1 & Figure 4-6.2). A 98-day delay in starting targeted vaccination, results in 330,907 total cases with a vaccine with 35% efficacy and 303,451 total cases with a vaccine with 70% efficacy (Table 4.6-1 & Figure 4.6-2). Finally, a targeted vaccination campaign starting on day 127, results in a cumulative total of 401, 509 cases and 397,489, with a vaccine with 35% and 70% efficacy, respectively (Table 4.6-1 & Figure 4.6-2).

Our results show that a targeted vaccination strategy can reduce the number of total cases when compared to the base-case scenario. However, early implementation of this strategy can result in a prolonged epidemic, which may have unintended economic impact. Delayed implementation of this strategy also reduces the total number of cases, but the number of cases increases as the starting day is delayed. Nevertheless, under a uniform death rate, the suggestion of vaccinating children and elderly is not a very effective response strategy. Furthermore, the simulations demonstrate that both levels of vaccine efficacy, 35% and 70%, result in similar benefits. Therefore, early production of less-effective vaccine would provide better consequence mitigation than later production of more-effective vaccine.
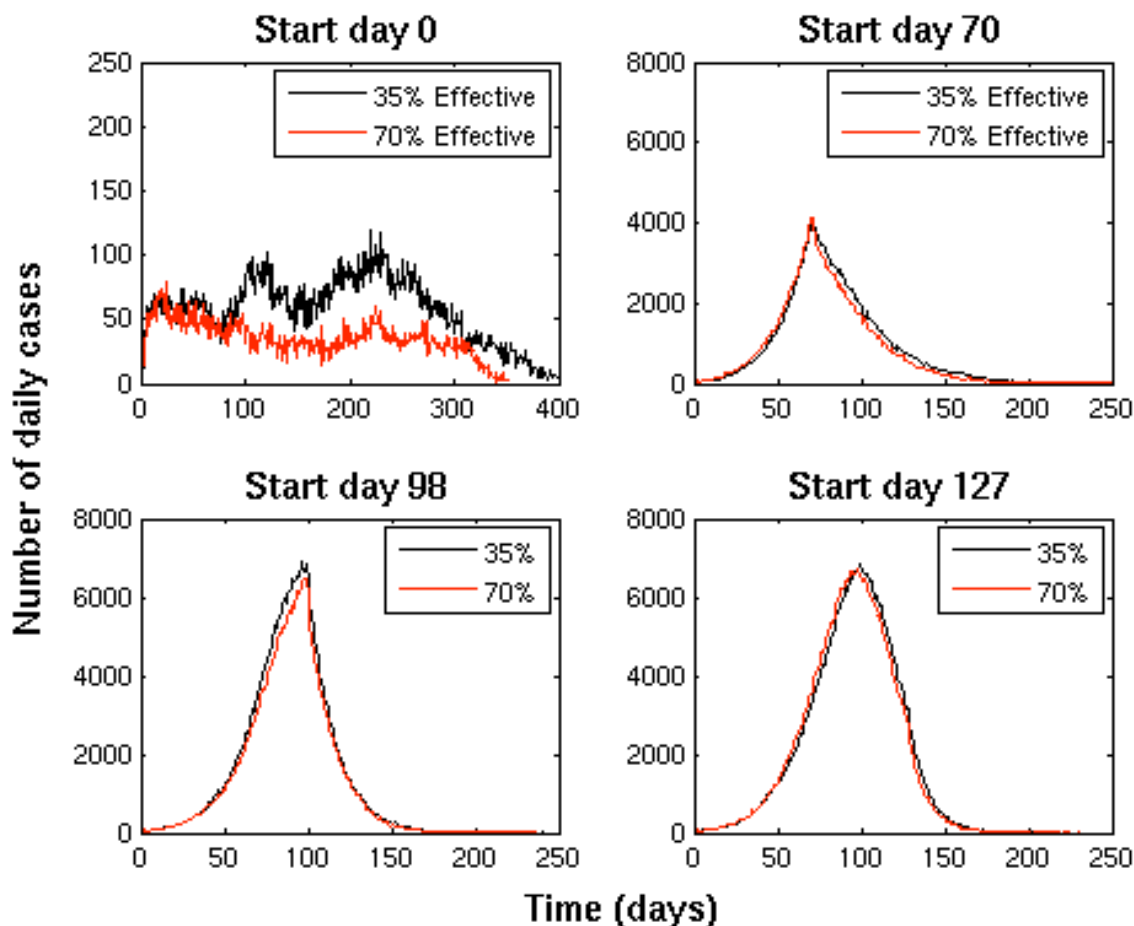
Figure 4.6-2. New influenza infections per day, with vaccination of 20% of population targeted to children and seniors, for nominally- and partially-effective vaccine, for various delays in vaccine delivery.

4.6.5 Impact of Partially-effective Antivirals for 2% of the Population

The currently available antivirals have proven to be effective in preventing infection, reducing symptoms, shortening the infectious period, and reducing the probability of transmission. However, since we do not know whether the future pandemic flu virus will be similar to the viruses where the antivirals have been tested on, we considered two levels of antiviral efficacy. The 70% effective strategy assumes that antivirals prevent 70% of infections, shortens those infections that do occur by one day, and reduces the infectiousness during the infectious stage by 80%. The 35% effective strategy assumes that antivirals prevent 35% of infections, shortens those infections that do occur by half a day, and reduces the infectiousness during the infectious stage by 40%.

The U.S federal government reportedly has ordered 5.3 million courses of oseltamivir for Strategic National Stockpile. Therefore, in our simulations we

consider a 2% limited antiviral supply. The 2% antiviral supply is distributed to the population in the following manner: 1) persons with influenza symptoms, and 2) named contacts for such symptomatic persons, in particular individuals in the same household, school, or workplace. However, since it may not be feasible to trace every contact of each infected individual, we assume that the fraction of contacts that are found for the different social settings are: 90% household contacts are found, 90% visiting, 80% work, 80% school, and 80% college.

A ring delivery of antivirals program can stop an influenza pandemic within 42 days with a 35% antiviral efficacy, and within 21 days with a 70% antiviral efficacy (Table 4-6.1). Figure 4-6.3 shows the number of daily cases for both antiviral efficacies. Our results show that timely ring delivery of even partially effective antivirals is more effective than any other intervention analyzed in this study. Although, ring delivery would be hard to implement, given the short incubation period of influenza, under a limited resource scenario, it should be considered.
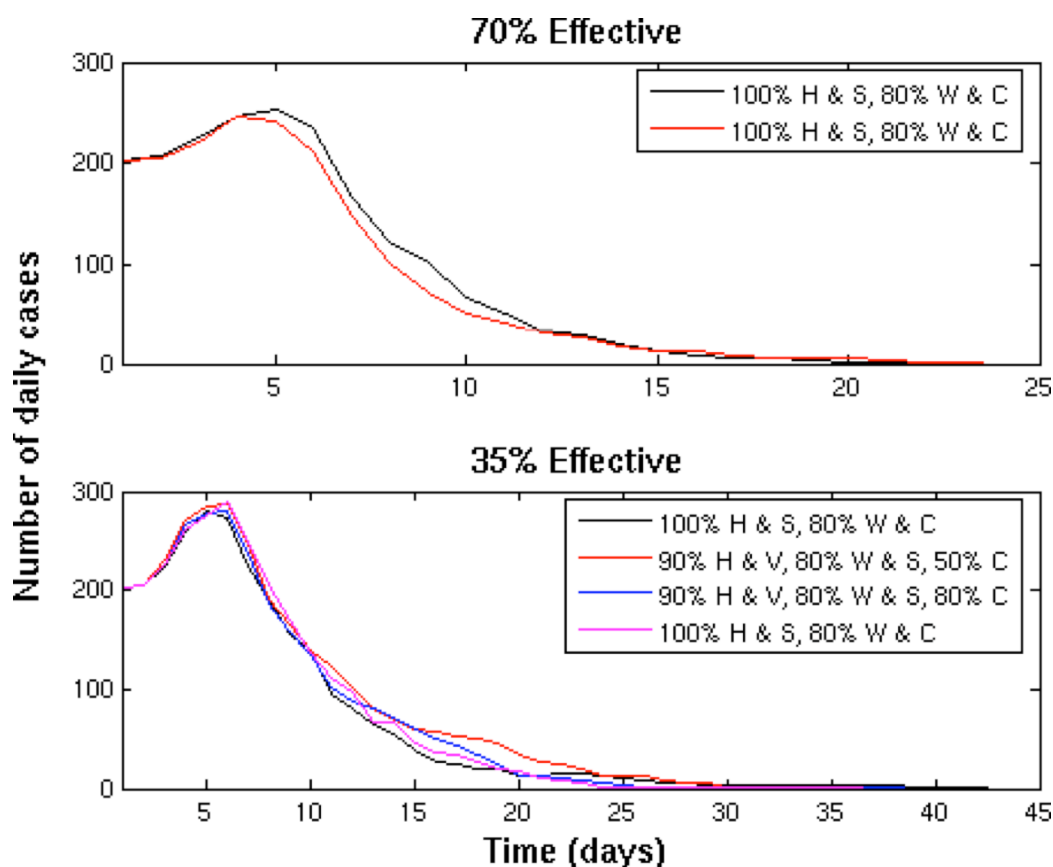
Figure 4.6-3. Current number of infected persons, with partially-effective antivirals for 2% of the population delivered on day 0, for various fractions of people found through contact tracing (H: home, W: work, C: college, V: visiting, S: school).

Table 4.6-1. Summary of Interventions and Results

Intervention	Cases	Deaths	Doses	Final day[a]
None	420,274	5,611	-	283
40% mass vaccination (35% effective) after *t* days				
t = 0	2,852	29	646,347	135
t = 70	157,776	1,922	646,353	215
t = 98	298,245	3,832	646,345	203
t = 127	394,233	5,185	646,349	195
40% mass vaccination (70% effective) after *t* days				
t = 0	1,852	21	646,347	139
t = 70	142,586	1,823	646,344	243
t = 98	295,024	3,845	646,345	228
t = 127	383,875	5,055	646,344	211
20% mass targeted vaccination (35% effective) after *t* days				
t = 0	23,124	292	323,171	400[b]
t = 70	211,319	2,694	323,182	314
t = 98	330,907	4,282	323,174	246
t = 127	401,509	5,328	323,187	222
20% mass targeted vaccination (70% effective) after *t* days				
t = 0	12,691	160	323,171	300[b]
t = 70	197,151	2,560	323,187	265
t = 98	303,451	3,946	323,176	243
t = 127	397,489	5,264	323,172	235
2% ring delivery antivirals at *t* = 0				
35% effective	530	2	30,259	42
70% effective	377	2	29,480	21

Cases, deaths, doses, and effectiveness of interventions with 202 initial cases in the city of Portland, consisting of 1,615,860 people. The results are based on a typical stochastically simulated pandemic influenza with a clinical attack rate of 25%.
[a] Day from infection of index cases until outbreak is controlled (when the number of cases is 0). [b]Epidemic still has a few people infected.

4.6.6 Discussion

The present investigation shows that an influenza pandemic may be controlled by means of ring delivery of antivirals, and early distribution of vaccines. However, given the unlikely event of having a pandemic flu vaccine, distribution on day 0, is an extremely optimistic assumption for the first wave of the epidemic. Therefore, case isolation, contact tracing, and timely distribution of antiviral seem to be the best strategy in containing a pandemic.

The four most important policy implications from the model results are:

1) Delay in intervention will dramatically increase the total number of cases and deaths.
2) Timely ring delivery of limited antivirals can reduce the number of cases and shorten the epidemic drastically.
3) Partially effective vaccines have similar effects in the overall impact of the epidemic; therefore, delaying manufacturing to produce a more effective vaccine may not be worth it.
4) Timely targeted vaccination of children and elderly can prolong the epidemic, resulting in a greater economic impact.

4.7 Nationwide Analysis of Consequence Mitigation Strategies Using EpiCast Model

EpiCast is an agent-based model for the United States that captures the transmission of the virus in different mixing groups like community, work-places, household clusters, schools, and households. In this large-scale model the 280 million agents are distributed among 5 age groups according to demographic data. The geographic distribution is represented by about 60,000 tracts (each containing about 5000 people) and movement of people between the tracts, whereby the movement is given by data from the transportation bureau and can be split into daily commuter travel to work and longer distance travel (business trips, vacation, etc.). By fitting the model parameters to different aggressive strains –as represented by the basic reproductive number R_0 (basically the number of persons a sick individual infects directly) – of the hypothetical virus, several mitigation scenarios for different virus strengths could be investigated. Preliminary results suggest that for reproductive numbers R_0 less than 2.0, targeted administration of antiviral drugs helps to control the spread until vaccine is developed. For more aggressive viruses a more sophisticated combination of measures is necessary to control the spread.

The simulations were run on large multi-processor machines. Simulations assume the ongoing daily entry of a small number of incubation-stage individuals through several major international air hubs in the continental US, resulting in a typical pandemic outbreak (in the absence of any intervention strategies) as shown in Figure 4.7-1.
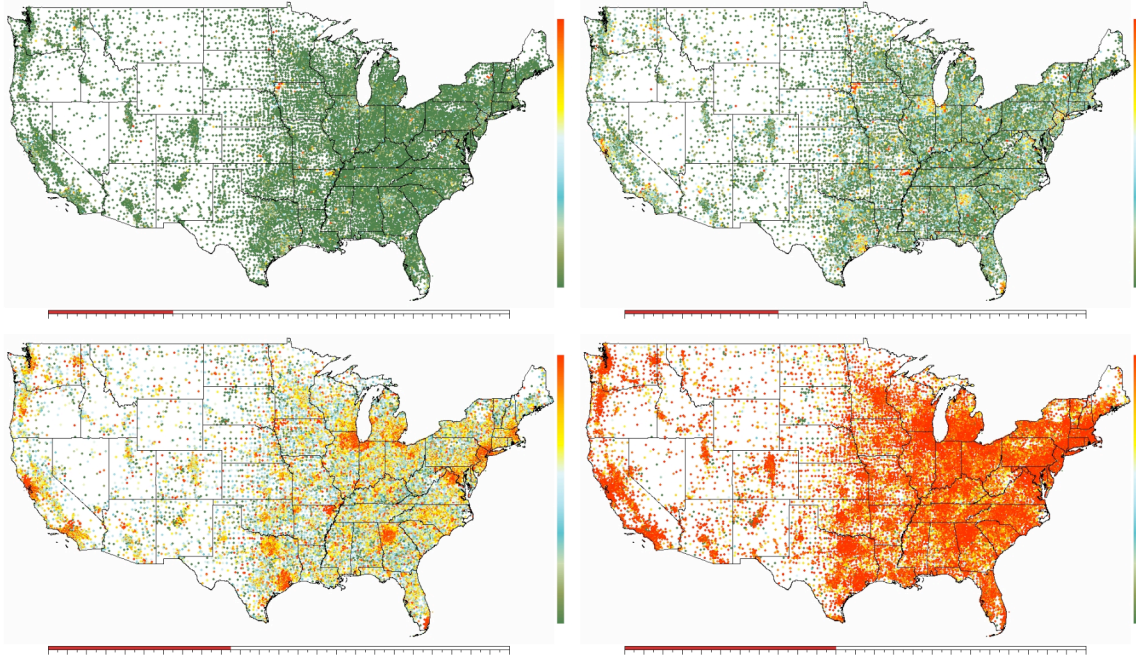
Figure 4.7-1. Baseline simulation realization of a pandemic flu outbreak with $R_0 = 1.6$, introduced by the daily entry of a number of infected individuals through 14 major international airports in the continental U.S. (beginning on day 0). The spatiotemporal dynamics of the prevalence (number of symptomatic cases at any point in time) is indicated on a logarithmic color scale at the right edge of each figure, from 0.3-30 cases per 1,000 residents. Snapshots are shown at (left to right, top to bottom) day 65, 80, 95, 110. Each dot on the map represents a tract containing on average of 5000 people; therefore the population density is indicated by the dot density.
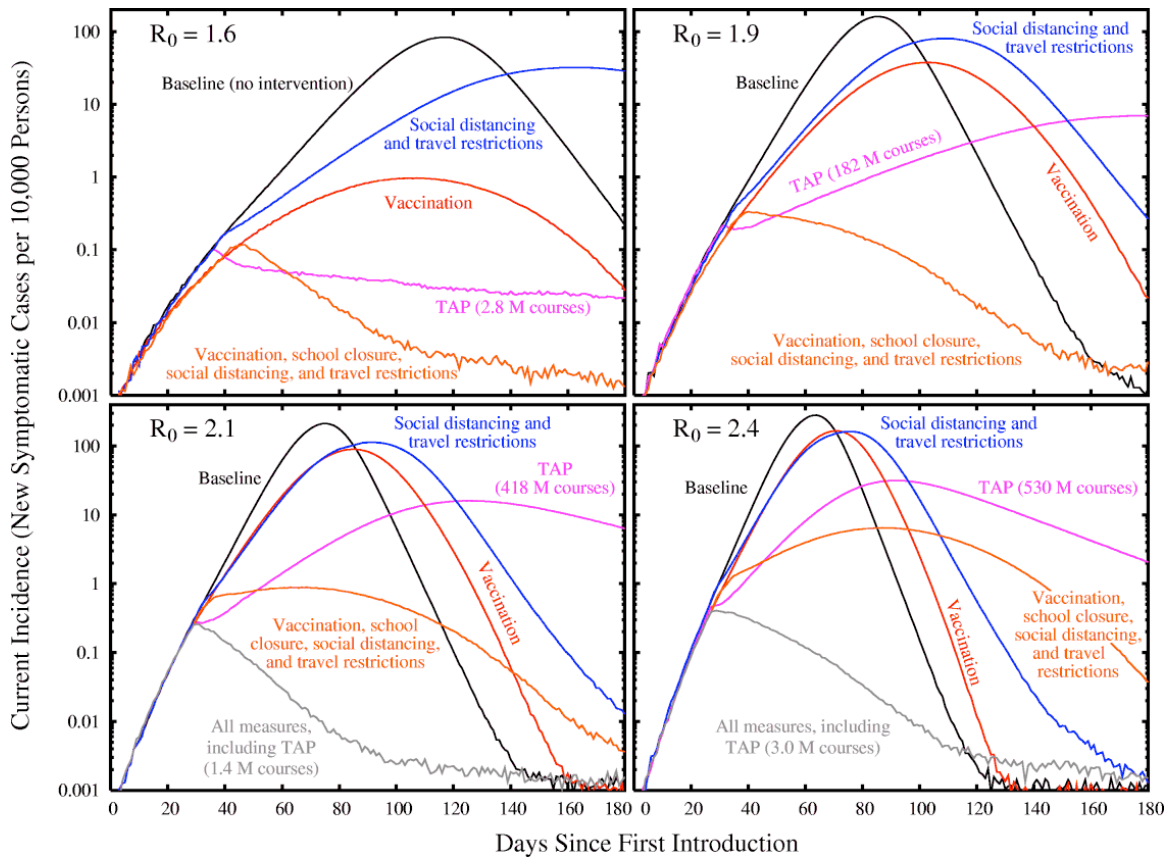
Figure 4.7-2. Nationwide epidemic curves with various consequence mitigation strategies, computed with EpiCast

A variety of mitigation strategies and their combinations have been studied using EpiCast[14]. In addition to mass vaccination and treatment of named contacts of diagnosed cases with antiviral medications (TAP, or targeted antiviral prophylactic treatment), these include the reduction of travel, school closure, non-essential work closure, and other social distancing measures, up to a mandatory quarantine. The nationwide epidemic curves for several of these mitigation strategies (including combinations of multiple strategies) are shown in Figure 4.7-2 above.

These results suggest that for reproductive numbers R_0 less than 2.0, targeted administration of antiviral drugs helps to control the spread until vaccine is developed, produced, distributed, and had time to produce an immune response. For more aggressive viruses, a more sophisticated combination of therapeutic and social distancing measures (including quarantine, school closure, and/or travel restrictions) is necessary to control the spread.

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[14] Germann, T.C., K. Kadau, I.M. Longini, and C.A. Macken, "Mitigation Strategies for Pandemic Influenza in the United States," submitted to *Science*.

Drastic restrictions on nonessential long-distance travel, to as little as 1-10% of the normal rates, were also studied, as shown in Figure 4.7-3. Although the final attack rate is completely unaffected by such a strategy, it is useful in delaying the spread from the initial sites of introduction to the rest of the country by as much as a month or two, depending on R_0 and the level of travel reductions.
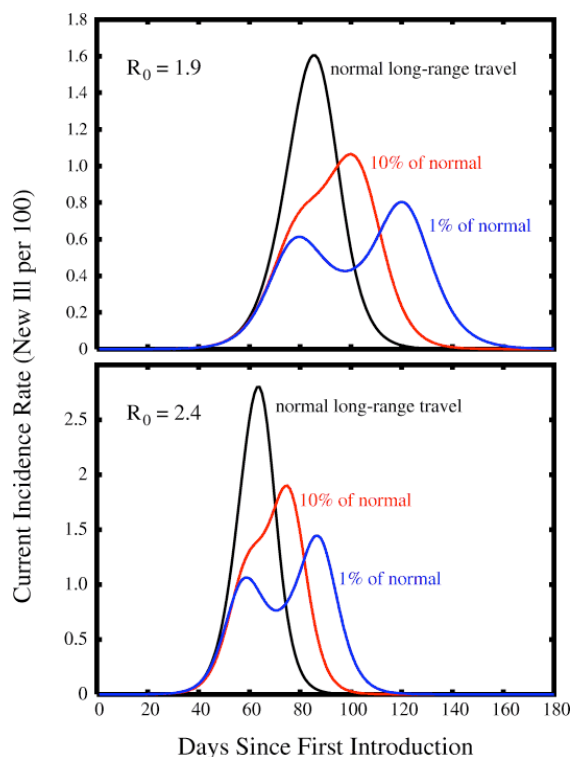
Figure 4.7-3. Nationwide epidemic curves with various reductions in nonessential long-distance travel, as computed with EpiCast.

These simulations also highlight the need for rapid characterization of a potential pandemic strain, including such basic quantities as the transmissibility R_0 and the serial interval (time between successive generations). Any model-based assessment of proposed intervention strategies will depend critically upon these parameters, which thus far have only been estimated based upon past (1918, 1957, 1968) pandemic strains.

5 Economic impacts

5.1 Categories of Economic Shocks

An Avian Influenza (AI) pandemic will have dramatic and permanent impacts on U.S. households and industrial output. Not only will a wide range of industries and infrastructure be interrupted in the short run, but the underlying population and work force could decrease in absolute terms by as much as 0.5 percent. As illustrated by Figure 5.1-1, morbidity and mortality from an AI pandemic will affect the labor and productive parts of the economy.
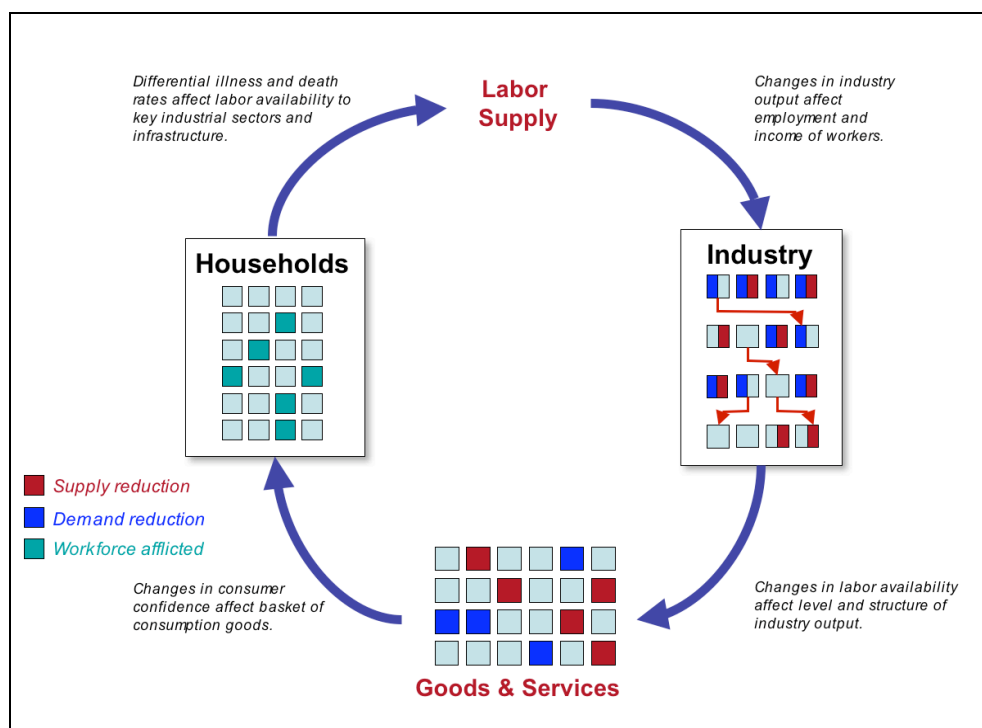
Figure 5.1-1. Circular-Flow Macroeconomic Framework

Households provide labor to the productive sectors of the economy, which then produce goods for intermediate use and final consumption. Given that the pandemic may infect the supply of labor along industrial and demographic lines, there particular industries could be hit harder than others (for example "blue collar" versus "white collar"). Likewise, the uncertainty related to the scope of infection and economic consequence (income, job security) will cause consumers to change their purchases, thereby affecting demand for particular goods and ultimately changing industry output, employment, and per capita income.

An AI pandemic is likely to have three direct economic impacts or "shocks" to the economy: (1) a reduction in the working and consuming population, (2) a reduction and restructuring of demand for particular goods and services, and (3) a loss of economic output and capacity (due to lost labor). The colored legend represents these economic shock categories. Dark green households on the left-hand side of the Figure 5.1-1 represent laborers who experience morbidity and mortality as a result of the pandemic. Their absence from the workplace results reduced labor supply represented in red across the top of Figure 5.1-1. Many workers are not covered by paid sick leave and therefore suffer income reduction when they don't work. This, together with a general trend towards short-term buyer conservatism and workers who suffer mortality results in a decline in demand for certain types of goods, usually consumer durables. This is represented in blue across the bottom of Figure 5.1-1.

5.1.1 Population Shocks

A fraction of those with AI will die. Loss of population over and above the normal and regular influences (births and deaths) in a large population represents a shock with long-term effects to the economy and the country as a whole. The age, sex, gender, and racial distribution of those who die will directly determine what part of the economy is hurt most.

5.1.2 Demand Shocks

As seen with the SARS outbreak in East Asia, a major economic impact will be the response of consumers to the outbreak itself and associated uncertainty about one's future.[15] Industries with significant face-to-face transaction (mass-transportation, restaurants, tourism) will see a sharp decrease in customers and overall demand. Consumers may delay non-essential travel in an effort to reduce exposure to illness. Analysis of recent cataclysmic events indicates that consumers will delay big-ticket expenditures such as furniture, major appliances, automobiles, and housing.[16] These demand shocks will have a direct impact on industry sales and employment.

In addition to curtailing purchase of durable goods, consumers might be induced to hoard non-durable, consumables such as food. Hoarding is frequently observed, for example, in areas subject to hurricanes; people empty the shelves of grocery

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[15]See, for example, Fan, E. "SARS: Economic Impact and Implications." *ERD Policy Brief No. 15, Economics and Research Department, Asian Development Bank, Manila.* 2003.
Lee J. W. and W. McKibbin. February 2004. "Globalization and Disease: The Case of SARS," Brookings *Discussion Papers in International Economics*.
Lin, Yi-Chun, "Impact of an Epidemic on the Medical and Economic Systems - The Case of SARS Outbreak in Taiwan." *Asian Development Outlook 2005.* Hong Kong, China: Oxford University Press for the Asian Development Bank.
[16] See, for example, ATA Working Group, "Potential Economic Impacts of a MANPAD Attack on Civil Aviation," draft memo, March 17, 2003; see also Richard Curtin "Consumer Confidence in the 21st Century: Changing sources of Economic Uncertainty." Survey Research Center. University of Michigan. October 2002. http://www.sca.isr.umich.edu/documents.php?c=s .

stores and line up at gas stations anticipating that they may not be able to obtain such items after the storm hits. While hoarding can have economic consequences its main effect is likely to make purchases now in exchange of those in the future.

Finally, while the overall national economy tends to rebalance consumption to other categories, and labor moves from declining to advancing industries, some sectors of the economy could be acutely damaged. For example, the poultry industry will be affected significantly, as consumers reduce their consumption of chicken (in favor of beef, pork, and fish) and chicken producers cull their stock.

5.1.3 Supply Shocks

As the pandemic advances, absenteeism in the work place will increase due to (1) actual illness, (2) absenteeism to care for individuals who are ill, and (3) voluntary quarantine due to fear of becoming ill. This will collectively result in a reduction in the labor force, a reduction in output of goods and services, and a loss of income to wage earners.

Absenteeism will also impact infrastructures, especially those that involve frequent human-to-human contact; these include transportation, health care, and emergency services. Electric power outages might result from the inability to keep sufficient labor on the job to maintain equipment and facilities; power outages would affect other key infrastructures such as communications, water, and transportation.

5.2 Estimates of Economic Impact

Three sets of simulations were conducted, reflecting three different pandemic scenarios: a "*most likely*" scenario that represents the best information on pandemic effects and economic response, and a "*less severe*" and "*more severe*" scenario. The each scenario models an AI pandemic that runs through a six- to eight-month cycle and then affects the economy directly and indirectly for up to 10 years.

5.2.1 National Impacts

Our measures of national economic impact are the changes of Gross Domestic Product, Employment, and Income per Capita. Table 5.2-1 lists the impacts to the nation in the initial year of the outbreak and the 10 years that follow.

Table 5.2-1. National Economic Impacts of AI Pandemic: Various Scenarios

Economic Variables/ Scenarios	Year					
	1	2	3	4	5	10
Gross Domestic Product (Billions of Fixed 1996$ and %)						
Less-severe Scenario	-258 (-3%)	-31 (-0.3%)	-26 (-0.3%)	-20 (-0.2%)	-16 (-0.1%)	-14 (-0.1%)
Most-likely Scenario	-593 (-6%)	-71 (-1%)	-60 (-1%)	-44 (-0.4%)	-34 (-0.3%)	-30 (-0.1%)
Severe Scenario	-1190 (-12%)	-152 (-2%)	-132 (-1%)	-101 (-1%)	-83 (-1%)	-76 (-0.5%)
Employment (Thousands and %)						
Less-severe Scenario	-3,892 (-2%)	-486 (-0.3%)	-384 (-0.2%)	-268 (-0.2%)	-204 (-0.1%)	-166 (-0.1%)
Most-likely Scenario	-8,882 (-5%)	-1,095 (-1%)	-862 (-1%)	-587 (-.4%)	-436 (-.2%)	-340 (-.2%)
Severe Scenario	-18,100 (-11%)	-2,355 (-1%)	-1,928 (-1%)	-1,388 (-1%)	-1,090 (-0.5%)	-900 (-0.5%)
Per-Capita Income (Thousands Fixed 1996$ and %)						
Less-severe Scenario	-0.4 (-2%)	0 -	0 -	0 -	0 -	0 -
Most-likely Scenario	-0.9 (-4%)	0 -	0 -	0 -	0.03 (0.1%)	0.03 (0.1%)
Severe Scenario	-2 (-8%)	0.02 (0.1%)	-0.01 (-0.05%)	0.03 (0.1%)	0.05 (0.2%)	0.06 (0.2%)

The most-likely scenario will cause an estimated $600 billion loss in GDP, or about six percent of GDP, in the year of the pandemic, and a loss of almost nine million jobs. In component terms, the supply shocks (the reduction in productivity and employment) contribute the largest share impact, with a loss of $350 billion (3.7%) of GDP and 4.5 million jobs. The demand shock (the reduction in spending on goods and services) is also quite significant, causing the loss of about $230 billion in GDP (2.4%) and a loss of approximately 4 million jobs. Finally, the population shock (the loss of life) contributes $28 billion to this loss in the first year and grows steadily through year 10 to $37 billion. While this may seem a relatively small annual change, it is a relatively permanent condition and results in reduced present value of GDP of $274 billion over a ten-year time horizon.[17] As shown in Figure 5.2-1, this population shock is small in the first year but very significant in the follow on years.
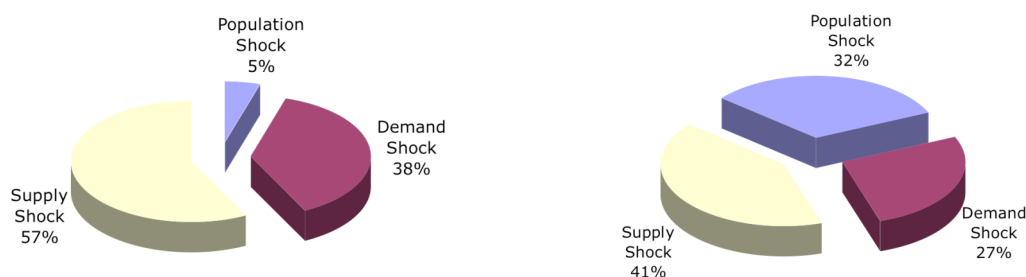
Figure 5.2-1. Sources of Impacts: First Year (left) and 10 Years (right)

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[17] Discounted at a real discount rate of 3.6% as recommended by OMB.

The results suggest that recovery from such an event may take five years for the medium scenario. The population effect will remain throughout the run, which will have a more lasting effect on the country's supply and demand for goods and services. Industries that will be most affected are given in Figure 5.2-3 (below) for the most-likely scenario. The effects range from a 4% loss of output to a 15% loss in output. Service industries and other labor-intensive industries feel the population loss the most.

The population shock causes a permanent structural change to the economy. In a very real sense, the population and economy are permanently on a different growth trajectory than before the outbreak. The demand and supply shocks, on the other hand, are temporary: the economy bounces back in the year after the pandemic. Figure displays percent difference between the U.S. economy subject to an AI pandemic and the baseline U.S. economy over the 10-year forecast period. In the first year of the pandemic, national output, employment, and per capita income experience significant reductions due to the population, demand, and supply shocks. By year 2, however, the majority of the demand and supply shocks (caused by AI morbidity) have subsided, leaving only the population shock (caused by AI mortality). As the figure shows, the reduction in population has permanently reduced the economic capacity of the country.
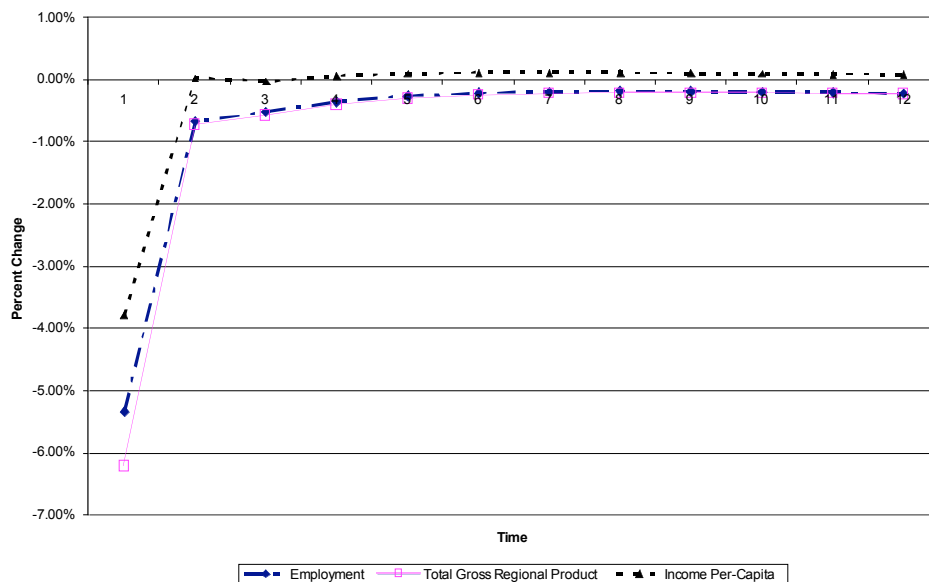
Figure 5.2-2: Percent Change in Economic Variables for Most-Likely Scenario

While by definition not as likely as the previous scenario, the less and more severe scenarios provide a working range of results that quantify the uncertainty about exactly how a real pandemic would evolve and what the economic impacts would be.

5.2.2 Impacts by Industry

Figure shows the loss of output in the first year, by industry.[18] Industries suffering large output declines include arts and entertainment, mining, government services, finance and insurance, retail trade and forestry. The total loss of output in each industry is a function of the total number of workers lost to morbidity and mortality, the change in demand due to consumer uncertainties, and how critical labor is to the output of an industry (e.g., in the Mining industry). The industry hardest hit by the pandemic is the Educational Services sector which suffers an almost 14% decline in output. Demographically, this sector employs large numbers of people who will be absent from the workplace.[19]
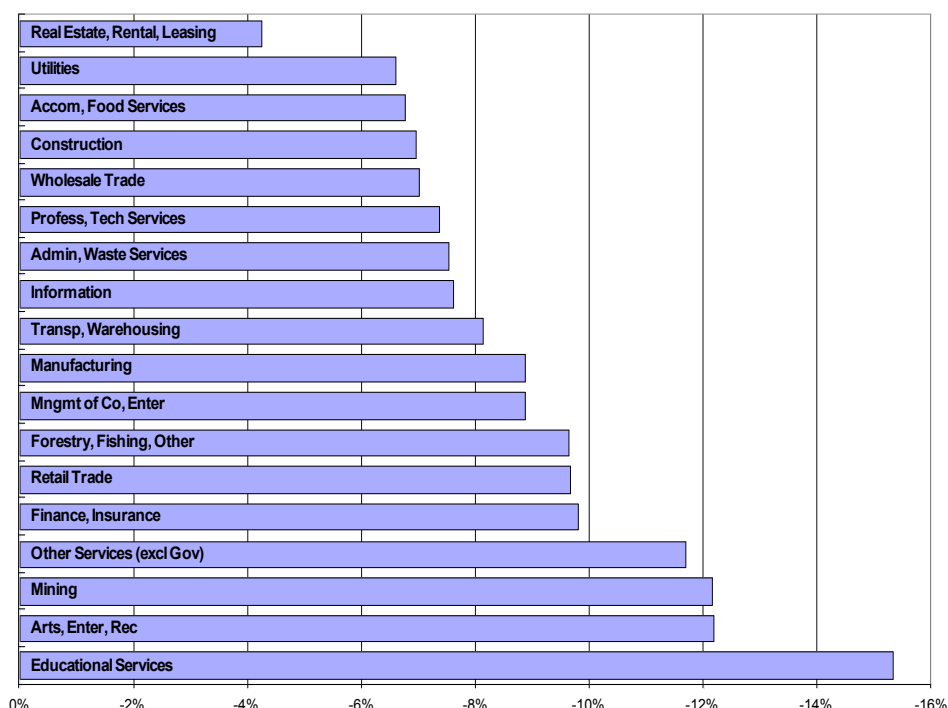
Figure 5.2-3. Percent Changes in GDP, by Industry: First Year, Most Likely Scenario

In contrast, the effect of reductions in demand for Accommodation and Food Services (as consumers try to avoid exposure to the virus by staying home and cooking their own food) was not as large as those in other industries. This is due in part to the effects that industries have on each other: while the direct shocks to the Food Service industry are large, the indirect effect of losses in other industries *on* food services is relatively small. Consider instead the modeled shock to automobile and other durables goods purchases which is part of the Manufacturing sector in **Figure** . Losses to the automobiles part of the Manufacturing sector have very large *indirect* impacts to other manufacturing

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[18] The industries shown are each a collection of NAICS (North American Industrial Classification System) industries.

[19] The language in the reference (most likely) scenario does consider real possibility that educational institutions would be closed during a pandemic.

industries, since any loss in automobile sales reduces the demand for and output of a wide range of industries, such as glass, steel, machinery, electronics, and other automobile components; this collective loss on the manufacturing industry is much greater than the collective loss on the accommodation and food service industries.

Table 5.2-2 groups the multi-year loss of GDP shown in Figure by industry and by descending level of first-year impact. The table shows that most industries follow the recovery path of the overall economy, but with several relatively unimportant exceptions. First, the construction industry experiences larger declines for the first 5 years, since most industries reduce their investment (and thus construction) as a response to the loss of output; in year 10, however, the restructuring of the economy has spurred new investment (and thus construction) in new sectors of the economy.

Table 5.2-2. Change in GDP: Various Years, Most-Likely Scenario

| Industry	Year / Percent Loss of GDP					
	Outbreak	2	3	4	5	10
Educational Services	-15%	-0.3%	-0.4%	-0.2%	-0.2%	-0.1%
Arts, Enter, Rec	-12%	-0.4%	-0.4%	-0.3%	-0.2%	-0.2%
Mining	-12%	-2.0%	-1.0%	-0.7%	-0.4%	-0.1%
Other Services (excl Gov)	-12%	-0.5%	-0.4%	-0.3%	-0.2%	-0.2%
Finance, Insurance	-10%	-0.5%	-0.4%	-0.3%	-0.2%	-0.2%
Retail Trade	-10%	-0.5%	-0.5%	-0.3%	-0.3%	-0.2%
Forestry, Fishing, Other	-10%	-1.0%	-0.8%	-0.4%	-0.2%	-0.1%
Mngmt of Co, Enter	-9%	-0.8%	-0.6%	-0.4%	-0.3%	-0.2%
Manufacturing	-9%	-1.0%	-0.8%	-0.5%	-0.4%	-0.3%
Transp, Warehousing	-8%	-0.7%	-0.5%	-0.4%	-0.3%	-0.2%
Information	-8%	-0.6%	-0.5%	-0.4%	-0.3%	-0.2%
Admin, Waste Services	-8%	-0.6%	-0.5%	-0.3%	-0.3%	-0.2%
Profess, Tech Services	-7%	-0.8%	-0.6%	-0.4%	-0.3%	-0.2%
Wholesale Trade	-7%	-0.7%	-0.6%	-0.4%	-0.3%	-0.2%
Construction	-7%	-3.0%	-2.0%	-0.8%	-0.3%	0.1%
Accom, Food Services	-7%	-0.4%	-0.4%	-0.3%	-0.2%	-0.2%
Utilities	-7%	-0.6%	-0.5%	-0.4%	-0.3%	-0.2%
Real Estate, Rental, Leasing	-4%	-0.5%	-0.5%	-0.4%	-0.2%	-0.2%
Health Care, Social Asst	5%	-0.4%	-0.4%	-0.3%	-0.3%	-0.3%

Figure .2-4 converts the data shown in Table 5.2-2 to a line graph. Notice that health care is the only industry experiencing growth in the first year of the simulation, as indicated in the scenario. After the first year shock output of the health care industry returns to a level close to its pre-shock level. However, as with all industries, the health care industry output is slightly lower than before the shock due to the permanent demographic effect of the mortality associated with the AI outbreak.
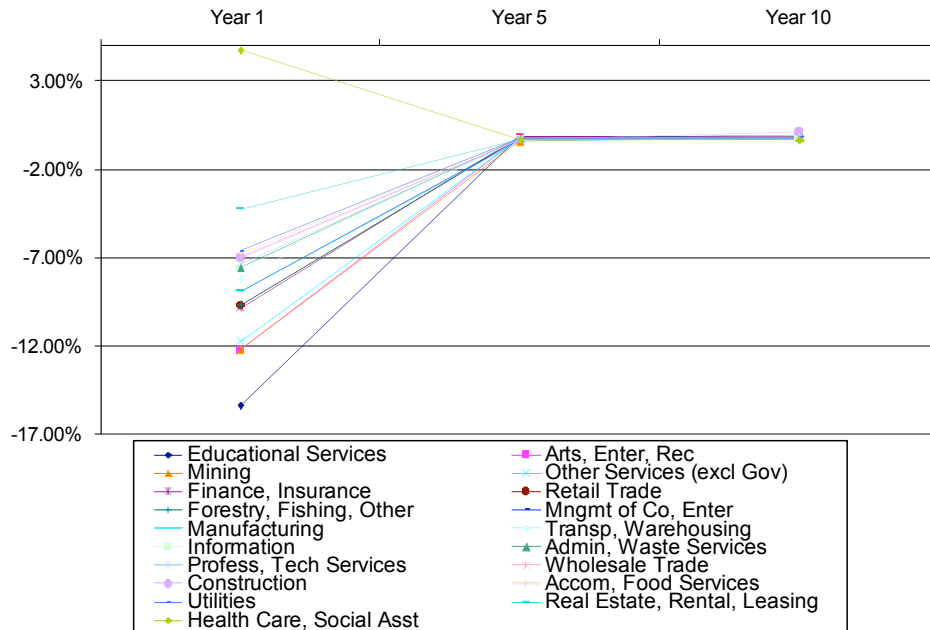
Figure 5.2-4. Dynamic Adjustment to AI Shock

Finally, Figure shows the loss in GDP in each state in the first year of the pandemic. While losses do correlate weakly with the size of the state, i.e., California and Texas suffer large losses, smaller states such as Alabama and the Carolinas do suffer large percent losses of output.
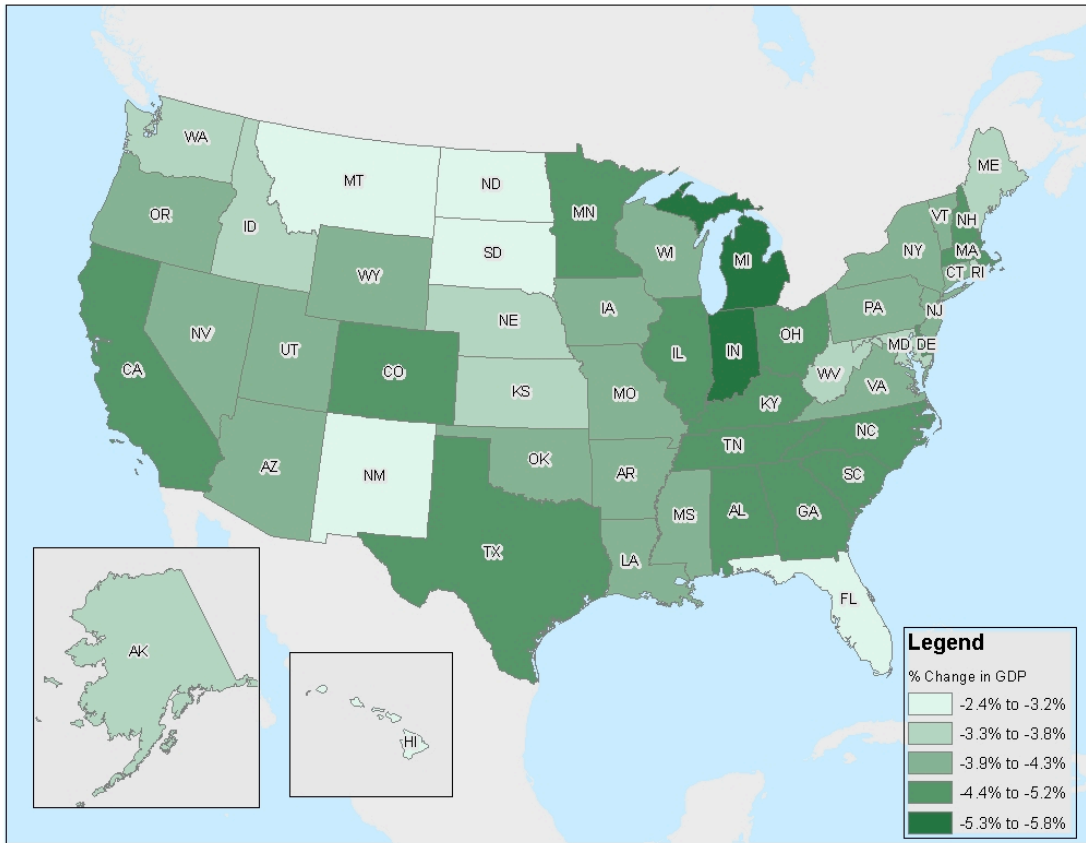
Figure 5.2-5. National Loss in GDP, by State: First Year, Most Likely Scenario

This is likely due to the combined effects of the population shock and the demand shock. Alabama, the Carolinas, Ohio, and Michigan have significant automobile sectors; the loss of demand for durables such as Vehicles and Parts (see Table) has large impacts to these industrialized states. Florida, in contrast, experiences relatively little loss, in particular given its size (it is the 4th-largest state in terms of population). This is likely due to the demographics of its working population and the less industrialized nature of its economy.

5.3 Modeling Inputs and Assumptions

To model the economic "shocks" and ensuing interdependencies in a structured and internally consistent way, REMI,[20] a dynamic macroeconomic model that can calculate how the economy adapts both by region and sector over the course of years, was used. Because REMI is an annual model (its finest resolution is one year), all economic shocks are converted to annualized values. Table lists the annualized economic shocks for each of the three scenarios.

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[20] REMI Policy Insight Model, Version 7.0. Regional Economic Modeling, Inc. Amherst, MA. www.remi.com.

Table 5.3-1. Shocks to the U.S. Economy: First Year, Various Scenarios

Avian Influenza Economic Shocks	Less Severe	Most Likely	More Severe
Demographic Shock: Loss of population[1]	500,000	1,000,000	2,500,000
Demand Shocks: Loss of demand for: [2]			
Vehicles and Parts	-4%	-8%	-15%
Computers and furniture	-4%	-8%	-15%
Other durables	-4%	-8%	-15%
Clothing and Shoes	-4%	-8%	-15%
Transportation	-4%	-8%	-15%
Medical Care	+4%	+9%	+13%
Other Services	-4%	-8%	-15%
Supply Shock: Loss of industrial output[3]	-1.0%	-2.5%	-5.0%

Notes to table: 1. Assumes 25% of population becomes ill and 1%, 2%, and 5%, respectively, of ill individuals die. This is then converted to a survival rate for input to REMI. The process generates approximately 500,000, 1,000,000, and 2,500,000 deaths, respectively. 2. Health Care spending increases due to illness while other spending categories decrease. 3. Illness and voluntary or enforced quarantine increase absenteeism in the work place and reduce worker availability and productivity. Percentage reductions shown are divided among productivity and employment variables approximately 2/3, 1/3, respectively.

The most-likely scenario text assumes that 25 percent of the population will contract Avian Influenza. In the most likely scenario, we assume that 2 percent of ill individuals will die from the disease, while the less severe and more severe scenarios assume 1% and 5% of ill individuals, respectively, will die. Since it is unclear at this time whether sub-groups of ages will be infected and die more than others, we ran simulations that tested the effects of mortality allocated proportionally across all age categories of the population or focused in the 20-40 age groups. In both cases, the pandemic will have a significant and sustained impact on current U.S. demography.[21]

In contrast to the permanent impact the flu pandemic has on the demographics of the US population, the impact on aggregate demand and supply in the economy will be temporary but nevertheless potentially very large. As listed in Table , in the first year of the pandemic, spending on goods and services in high-productivity, high-wage sectors such as automotive could decrease by as much as 15 percent.[22] Health care expenditures, on the other hand, would increase by as much as 13 percent.[23]

The scenario indicates that as many as 25 percent of workers may be absent from their workplaces for extended periods during the approximately eight-month duration of the

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[21] For comparison purposes it is estimated that more than 500,000 individuals died in the Spanish Flu outbreak in 1918. This occurred at a time when population density in the US was considerably lower than today; but, a mitigating circumstance as compared with today is the considerably more extensive and detailed knowledge of medicine and epidemiology.

[22] These assumptions are drawn from the work of Lee and McKibbin, and Lin (both footnoted earlier) who have studied the effects of SARS on consumption.

[23] The estimate of increased health care costs was drawn from: Meltzer, M., N. Cox, and K. Fukuda. 1999. "The Economic Impact of Pandemic Influenza in the United States: Priorities for Intervention." *Emerging Infectious Diseases* 5(5):659-71.

pandemic. Absenteeism will have an impact on firms' ability to maintain output.[24] We assume that two factors will affect output from industry: productivity (output per labor hour) and employment. For our most likely scenario we have allocated the total supply shock effect between these two variables, assigning approximately two-thirds of the total effect to productivity and the remaining one-third to reduced employment, based on the number of workers who are likely to have paid time-off for sick leave[25].

5.4 Sensitivity Analysis

To supplement the *most-likely* scenario we also ran simulations for *less severe* and *more severe* scenarios as explained early in this report. Other tests and sensitivity analyses were performed. We used two different versions of the REMI model in our analyses—a national version and a 50-region version. In order to ensure that the models were equivalent we ran tests with common inputs for both models and satisfied that both models yielded the same results for aggregate variables that we could test.

We also ran an alternative population scenario to analyze the impact of a different assumption regarding the age-class incidence of AI mortality. Recall that in the *most likely* scenario we distributed the approximately 1,000,000 fatalities proportionally among all age classes. For the alternative scenario we concentrated the mortality among the working-age population by distributing 750,000 fatalities proportionally in the 20 year to 50 year age group while the remaining 250,000 fatalities were distributed proportionally among the remaining age-classes.

6 Critical Infrastructure/Key Resource Impacts

"If we have an avian flu outbreak here and it is even half as bad as the 1918 flu, we will be enormously dependent on being able to get remote access for a large number of people, and keeping the infrastructure functioning is going to be a matter of life and death and we take it very seriously."

– Remarks made by Stewart Baker, Assistant Secretary for Policy, Department of Homeland Security, at *Anti-counterfeiting and Piracy Summit: STOPing the Theft*, National Chamber Foundation, November 10, 2005, Washington DC.

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[24] Reduced output may coincide with reduced demand in some sectors so that, consumers' postponing durable goods purchases may be in tune with reduced supply of such goods. However, in services and consumables industries, demand pressures might cause price increases as firms struggle to meet demand. Health care is one example of this phenomenon.

[25] Data for this was drawn from Bureau of Labor and Statistics 2003 National Compensation Survey, Benefit Statistics.

There are several fundamentals regarding the performance of infrastructures that need to be well understood in advance of any national-scale disruptive event that can point to those critical unknowns which need to be addressed – whether it is by the infrastructure provider, the infrastructure consumer, agencies of local, state and federal governance, or some combination of the above.

First, as is well known, infrastructures are very interdependent. The performance of the health care sector, for example, is highly reliant on the reliable supply of energy resources (e.g., electric power) to enable performance of life-saving equipment on a regular basis, and on the performance of the transportation infrastructure in all its facets (air, road, rail, and waterborne commerce) to provide just-in-time quantities of vital medical supplies. While these interconnections have redundancies in some cases (most hospitals have backup generators on-site) these redundancies are not universal and are not designed to be continuously tested for long durations of time. Therefore, in focusing on the vitality of the health care system, it is important to also consider the vitality of those systems on which the health care system is dependent.

Secondly, infrastructures are in substantive part privately owned. Infrastructure providers thus have responsibility not only to their customers (to provide a reliable level of service) but to their stakeholders (to maintain revenue streams and profitability expectations). Thus it is in the best interest of these infrastructures to plan for adverse contingencies where plausible, and to coordinate where necessary with other providers (both in the same sector as well as in dependent sectors) to avoid leaving 'gaps' in capability that could serve as congestion points in the productivity of the infrastructure.

Third, both public and private owners of infrastructure have well-known and recorded histories in dealing with unintended potential labor shortfalls, specifically strikes, lockouts, and work stoppages. In the last three years of data alone (2002-04) reported to the Bureau of Labor Statistics, 50 work stoppages involving 1,000 or more employees each, totaling over 8 million days of labor lost, have occurred throughout the United States. One need not look very hard to find examples of large-scale systems disruptions:

- In the food sector, a strike involving United Food and Commercial Workers and three California grocery chains involved up to 67,000 workers, began on October 12, 2003, and lasted 95 days.

- In the maritime transportation sector, a lockout of the International Longshore and Warehouse Union by the Pacific Maritime Association idled 10,500 workers at Pacific Coast ports for over a week.

- In the telecommunications sector, a strike in 2000 involving members of both the Communications Workers of America and the International Brotherhood of Electrical Workers and Verizon Communications involved 85,000 workers and lasted 18 days.

- In the surface transportation sector, a work stoppage in 1997 involving members of the Teamsters and UPS involved 180,000 workers, most of whom were out for 15 days.

Naturally, employers must prepare for these and other eventualities involving reductions in the availability of their work force as a part of regular business planning. Often this involves retraining of management to take action to meet particular vital tasks.

This type of preparation, already in-house at many infrastructure providers, can serve as a planning basis for defining critical tasks and roles, for identifying staff with primary, secondary, and tertiary responsibility for each task. When combined with coordination with other infrastructure providers as described above, these elements provide a basic requirements footprint necessary to satisfy the requirements on infrastructure as specified in Assistant Secretary Baker's statement above.

7 Additional References

Additional information on Relenza is available at
http://www.fda.gov/cder/consumerinfo/druginfo/relenza.htm.

More information on oseltamivir may be obtained at
http://www.fda.gov/cder/drug/infopage/tamiflu/default.htm.

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Appendix A. Glossary

TERM	DEFINITION	SOURCE
Amantadine	Orally administered anti-viral approved for treatment and prophylaxis of influenza A virus	CDC, Antiviral Agents for Influenza: Background Information for Clinicians, December 16, 2003
Antibody	An immunoglobulin, a specialized immune protein, produced because of the introduction of an antigen into the body, and which possesses the remarkable ability to combine with the very antigen that triggered its production.	MedicineNet.com
Antigen	A substance that is capable of causing the production of an antibody	MedicineNet.com
Attack Rate	A form of incidence that measures frequency of disease, chronic conditions, or injury in a particular population for a limited time, such as during an outbreak. In calculating attack rates, the numerator is the number of new cases of a health problem during an outbreak, and the denominator is the population at the beginning of the period.	CDC/Glossary of Epidemiological Terms
Attack Rate	The proportion of susceptible individuals exposed to a specific risk factor in a disease outbreak that become cases. For an infectious risk factor, the attack rate is the number of secondary cases occurring within the accepted incubation period divided by the number of susceptible individuals in a closed group exposed to the primary (index) case.	Clinical Epidemiology & Evidence Based Medicine Glossary
Attack Rate	A cumulative incidence rate used for particular groups observed for limited periods under special circumstances, such as during an epidemic.	On-line Medical Dictionary
Case-Fatality Rate	Cumulative incidence of death in the group of individuals that develop the disease over a time period (often unstated); a proportion, not a rate	Clinical Epidemiology & Evidence Based Medicine Glossary
Case-Fatality Rate	The proportion of people with a particular condition (case-patients) who die from that condition. In calculating case-fatality rates, the numerator is the number of people who die from the condition, and the denominator is the total number of people with the condition.	CDC/Glossary of Epidemiological Terms
Clinical Illness	A case of influenza that causes some measurable economic impact, such as one-half day of work lost or a visit to a physician's office.	CDC/NVPO/FluAid Home
Cull	To examine and pick out or reject items of a group that aren't up to standard. In the case of avian flu, flocks of birds are culled to extract any that are infected with the disease. Infected birds are usually slaughtered.	
Dyspnea	Shortness of breath, difficult or laboured breathing	On-line Medical

TERM	DEFINITION	SOURCE
		Dictionary
Epidemic	The occurrence of disease within a specific geographical area or population that is in excess of what is normally expected.	CDC/National Immunization Program/Glossary
Febrile	Feverish	MedicineNet.com
Gross Attack Rate	Gross attack rate is the percentage of population that becomes clinically ill due to influenza	CDC/NVPO/FluAid Home
Hemagglutinin	one of two types of protuberances that dot the outside of the each type-A flu virus. Hemagglutinin is responsible for binding the virus to the sialic acid "receptor" on the outside of a healthy human cell, enabling the virus to attach to the cell, slip inside it and begin making new viruses.	
High-Risk Group	Individuals categorized as high risk are those who have a preexisting medical condition (e.g., asthma, diabetes mellitus) that makes them more susceptible to developing medical complications due to influenza. High risk does not mean that those persons are more likely to contract a case of influenza. It means that if they do have a case of influenza, then they are more likely to have an adverse health outcome (e.g., outpatient visit, hospitalization) than those considered non-high risk.	CDC/NVPO/FluAid Home
Incubation Period	The period following exposure, when pathologic changes are not apparent, and ending with the onset of symptoms of an infectious disease.	CDC/Glossary of Epidemiological Terms
Infection	The growth of a parasitic organism within the body. (A parasitic organism is one that lives on or in another organism and draws its nourishment therefrom.) A person with an infection has another organism (a "germ") growing within him, drawing its nourishment from the person	MedicineNet.com
Infectivity	The proportion of people who are exposed to an agent and become infected, frequently represented as R_0	CDC/Glossary of Epidemiological Terms
ILI	Influenza like illness	CDC
Isolation	the separation of persons who have a specific infectious illness from those who are healthy and the restriction of their movement to stop the spread of that illness.	CDC
Latency Period	The period following exposure, when pathologic changes are not apparent, and ending with the onset of symptoms of a chronic disease.	CDC/Glossary of Epidemiological Terms
Macrophage	A large cell that helps the body defend itself against disease by surrounding and destroying foreign organisms (viruses or bacteria).	CDC/National Immunization Program/Glossary
Morbidity	Any departure, subjective or objective, from a state of physiological or psychological health and	CDC/Glossary of

TERM	DEFINITION	SOURCE
	well-being.	Epidemiological Terms
Mortality Rate	A measure of the frequency of occurrence of death in a defined population during a specified time interval	CDC/Glossary of Epidemiological Terms
Mortality Rate	The proportion of individuals in a population that die in a given period of time, usually a year and usually multiplied by a 10^n population size so it is expressed as the number per 1,000, 10,000, 100,000, ... individuals per year. These proportions are often broken into cause-specific and age-specific proportions and are often standardized so different groups can be compared and the population at the middle of the time interval is often used as the denominator.	Clinical Epidemiology & Evidence Based Medicine Glossary
Myalgia	Pain in a muscle or muscles	On-line Medical Dictionary
Neuraminidase	the second type of protuberance on the outside of the type-A flu virus. Neuraminidase neutralizes the remaining sialic acid on the outside of the target healthy cell, so when the compromised cell bursts, releasing the multiple new viruses that have been created inside of it, they can flow freely through the body, rather than being trapped by the cid.	
Neuraminidase Inhibitor	The neuraminidase inhibitors, zanamivir and oseltamivir, are chemically related drugs that block the active site of the influenza viral enzyme neuraminidase resulting in viral aggregation at the host cell surface and reduces the number of viruses released from the infected cell.	
Oseltamivir	the generic name for Tamiflu. It is an an antiviral drug and neuraminidase inhibitor that is used to treat infections caused by the influenza A and B viruses. Only available by prescription	
N-95 respirator	Filters out at least 95% of airborne particles	National Institute for Occupational Safety and Health
Pandemic		
Pathogenicity	The proportion of people who are infected by an agent and then develop clinical disease	CDC/Glossary of Epidemiological Terms
Pneumonia	Inflammation of one or both lungs with consolidation. Pneumonia is frequently but not always due to infection. The infection may be bacterial, viral, fungal or parasitic. Symptoms may include fever, chills, cough with sputum production, chest pain, and shortness of breath.	
Prophylactic	A prophylactic is a medication or a treatment designed and used to prevent a disease from occurring.	MedicineNet.com
Prophylaxis	A measure taken for the prevention of a disease or condition	MedicineNet.com

TERM	DEFINITION	SOURCE
Relenza	an antiviral drug for the treatment of the flu, known generically as zanamivir and also a neuraminidase inhibitor administered after infection occurs. It was developed by Australia's Biota Holdings and is produced and marketed by GlaxoSmithKline of Britain. Less well known than Tamiflu, Relenza is still seeing interests by governments worried about short supplies of the Roche drug, but because it is an inhaled drug, large-scale administration of Relenza could be complicated.	Wall Street Journal
Rimantadine		CDC, Antiviral Agents for Influenza: Background Information for Clinicians, December 16, 2003
	Orally administered anti-viral approved for treatment and prophylaxis of influenza A virus	CDC
Quarantine	Generally refers to the separation and restriction of movement of persons who, while not yet ill, have been exposed to an infectious agent and therefore may become infectious.	
Reye's Syndrome	A sudden, sometimes fatal, disease of the brain (encephalopathy) with degeneration of the liver, occurs in children (most cases 4-12 years of age), comes after the chickenpox (varicella) or an influenza-type illness, is also associated with taking medications containing aspirin. The child with reye's syndrome first tends to be unusually quiet, lethargic (stuporous), sleepy, and vomiting. In the second stage, the lethargy deepens, the child is confused, combative and delirious. And things get worse from there with decreasing consciousness, coma, seizures, and eventually death. The prognosis (outlook) depends on early diagnosis and control of the increased intracranial pressure.	
Social Distancing	Social distancing reduces contacts among individuals. It differs from a quarantine in that it may not affect all members of a household, and limited contacts may be permitted.	
Tamiflu	an antiviral drug for treatment of common human flu, made by the Swiss company Roche Holdings and administered after one has been exposed to the flu or begins to show symptoms. A neuraminidase inhibitor, it is known by the generic name oseltamivir. In the absence of an avian flu vaccine for humans, Tamiflu, which is administered as a tablet, is believed to be the only medication that can ameliorate symptoms, although in at least one case it has been ineffective against the disease.	Wall Street Journal
Virus	Obligate intracellular parasites of living but noncellular nature, consisting of DNA or RNA and a protein coat.	On-line Medical Dictionary
Virus	Molecules that hold only genetic material (DNA and RNA). Much smaller than bacteria, viruses are not alive (they do not eat or use oxygen). They lie dormant until they're absorbed into a living host, the only place they're able to reproduce, inside living cells. The diseases they cause can't be cured by antibiotics. Flu is a virus; it has eight genes that mutate rapidly.	Wall Street Journal

Appendix B. Antiviral Drugs and Vaccines for Influenza

Antiviral Drugs

Classes of Antiviral Drugs: Currently, there are four antiviral drugs licensed for the treatment of influenza in the United States. These drugs fall into two classes 1) adamantanes, (amantadine and rimantadine) and 2) the neuraminidase inhibitors (zanamivir, Relenza, and oseltamivir, Tamiflu). [1]

Usefulness for H5N1: The currently circulating strains of H5N1 found in Vietnam and Thailand are fully resistant to the adamantanes. [1] At this time, the neuraminidase inhibitors may improve prospects of survival, if administered early (within two days of symptoms), but clinical data are limited.[2] Currently, the neuraminidase inhibitors have low rates of drug resistance, but with increased use, drug resistance could increase. Of concern, the virus isolated from a case of avian influenza (H5N1) in a young girl in Vietnam was recently determined to be resistant to the drug oseltamivir (Tamiflu). This finding prompted the recommendation to consider stockpiling zanamivir, as well as oseltamivir. [3]

An older class of antiviral drugs, the M2 inhibitors amantadine and rimantadine, could potentially be used against pandemic influenza should a new virus emerge through reassortment.

For the neuraminidase inhibitors, the main constraints involve limited production capacity and a price that is prohibitively high for many countries. At present manufacturing capacity, which has recently quadrupled, it will take a decade to produce enough oseltamivir to treat 20% of the world's population. The manufacturing process for oseltamivir is complex and time-consuming, and is not easily transferred to other facilities.

Use in Pandemic Conditions: Use of antiviral drugs will depend on a number of factors including 1) the quantity and availability of the antiviral drugs, 2) the influenza pandemic strain and the characteristics of the pandemic it causes, 3) the potential for drug resistance of the pandemic strain or the development, and 4) the spread of antiviral resistance as the pandemic progresses[1]

Antibiotics for Secondary Bacterial infections, such as Pneumonia: To date, most fatal pneumonia observed in cases of H5N1 infection resulted from the virus, and therefore could not be treated with antibiotics. Nevertheless, because influenza is often complicated by secondary bacterial infection of the lungs, antibiotics could be life-saving for cases of late-onset pneumonia. WHO recommends countries have adequate supplies of antibiotics in advance. [2]

Use of Neuraminidase Inhibitors (Zanamivir, Oseltamivir) for Prophylaxis and Treatment: For treatment of influenza, oseltamivir is approved for ages one year and older, while Zanamivir is approved for ages seven years and older. When used within 48 hours of illness onset, both drugs decrease shedding and reduce the duration of influenza symptoms.

Studies of oseltamivir have shown a significant reduction in influenza-related lower respiratory tract complications (pneumonia and bronchitis) requiring antibiotic use and a significant reduction in hospitalizations. For both drugs, the recommended duration of treatment is 5 days.[4]

For influenza prophylaxis, oseltamivir is approved for use among persons aged 13 and older. Zanamivir has not been approved for prophylaxis. The duration of prophylaxis may vary. Long-term prophylaxis may last six to eight weeks, roughly corresponding to the average duration of the "flu season" in a community. Short term prophylaxis, of variable duration, may be recommended following a household or institutional exposure or for the period of time required for the development of protective immunity after vaccination.[4]

Recent concerns regarding Tamiflu safety: The FDA has evaluated reports of neuropsychiatric events (including 12 deaths) among Japanese children taking Tamiflu (oseltamivir) and concluded that this observation in Japan is "most likely related to an increased awareness of influenza-associated encephalopathy, increased access to Tamiflu in that population, and a coincident period of intensive monitoring adverse events". FDA determined that the data did not support a causal relationship between Tamiflu and the reported pediatric deaths. [5]

1) (http://www.dhhs.gov/nvpo/pandemicplan/, Annex 7: antiviral strategies and use, accessed November 17, 2005)
2) http://www.who.int/csr/disease/avian_influenza/avian_faqs/en/index.html, accessed November 17, 2005.)
3)   (Nature 437: 1108 , October 20, 2005.)
4)   http://www.fda.gov/cder/drug/antivirals/influenza/default.htm, Accessed November 30, 2005.
5)   http://www.fda.gov/cder/drug/infopage/tamiflu/QA20051117.htm, Accessed November 30, 2005.
6)   http://www.niaid.nih.gov/factsheets/fludrugs.htm, Accessed November 30, 2005.

H5N1 Vaccine Development and Production

Vaccines effective against a pandemic virus are not yet available. Vaccines are produced each year for seasonal influenza but will not protect against pandemic influenza. Although a vaccine against the H5N1 virus is under development in several countries, no vaccine is ready for commercial production and no vaccines are expected to be widely available until several months after the start of a pandemic.

Funds from the Strategic National Stockpile (SNS) have purchased approximately two million bulk doses of unfinished, unfilled H5N1 vaccine. This vaccine has not yet been formulated into vials, nor is the vaccine licensed by the HHS Food and Drug Administration. Clinical testing to determine dosage and schedule for this vaccine began in April 2005 with funding from NIH. Initial testing shows that, in its current form, a

much higher volume of vaccine, up to 12 times as much as originally predicted, will be needed in order to be effective.

The potential for virus mutation in reaction to prophylactic and treatment efforts adds another layer of uncertainty and complexity to effective use of vaccines.

- With conventional approaches, optimistic projections are that a vaccine to a pandemic strain could be produced within ~6 months (Schwartz and Gellin 2005).

- Given current US industrial capacity for large-scale pandemic vaccine production, US-based production for 1 year would be sufficient for full vaccination of only about one-half the US population assuming:
  - monovalent formulation with 15 micrograms of HA antigen (Stohr and Esveld 2004)
    - Research needed: Optimize amount of antigen needed per dose.
  - 2-dose schedule given a completely susceptible population (Leese and Tamblyn 1998).

- Major disadvantages to prophylactic vaccination and/or stockpiling vaccine based on current strain (Schwartz and Gellin 2005, Stephenson et al. 2004).
  - Pandemic could be caused by subtype other than H5 (e.g. H7 or H9).
  - Because of antigenic drift, the antigen that would be administered in vaccine will be different than the pandemic strain greatly reducing the efficacy of the vaccine.
  - Research question: how effective would a single dose of vaccine prepared before the pandemic would be in priming population or offering partial protection?
  - Research question: Develop a library of vaccine reference strains and reagents to anticipate pandemic strain.

Most, if not all of the most promising H5 vaccine candidates require the addition of an adjuvant agent that increases the antigenic response to achieve appreciable efficacy (Lipatov, et al. 2005, Stephenson, et al. 2005).

- An adjuvant is a substance that helps and enhances the pharmacological effect of a drug or increases the ability of an antigen to stimulate the immune system.
  - Issue to resolve: Many adjuvants are not currently licensed in the United States (Check 2005). Production capabilities for not having adjuvant added vaccines would be approximately 10 million doses per day during peak production.

- Reverse genetic systems seem to be the most promising alternative method to shorten vaccine development time (Check 2005, Webby et al. 2004).
  - Likely to produce the most rapid response in an emerging pandemic because exact desired vaccine strain can be engineered

- o Vaccines could potentially be produced within ~4 weeks of an emerging event, as compared to the ~6 months of conventional methods.
- o Prepare vaccine seed candidates containing target genes of potential pandemic viruses in advance of any specific threat.
- o Do not have to rely on the reassortment "lottery" used by conventional vaccine production in fertilized chicken eggs.
- o Regulatory, safety, and legal problems to surmount:
    - Mammalian cell lines used during process must be of certified quality for human vaccine production.
- o Have to find a way to circumvent "genetically modified organisms" classification which could impose regulations that could hamper R&D efforts.
- o Technology is patented, so licenses need to be granted for commercial development of the vaccines
- o Government purchase of patent, or subsidizing of licenses.

Appendix C: Case Fatality Rates for Pandemic Influenza

Case fatality rate: The proportion of individuals contracting a disease who die of that disease.

Influenza pandemics have occurred three times in the last century: in 1918 (Spanish influenza, H1N1), in 1957 (Asian Influenza, H2N2), and in 1968 (Hong Kong Influenza, H1N1). Of the three most recent pandemics, the 1918 pandemic was exceptionally severe, with mortality rates among the infected in the U.S. over 2.5%, compared to less than 0.1% in other influenza epidemics. The Asian flu of 1957–58 killed about one million globally and the 1968–69 Hong Kong flu was responsible for a global death toll of between one and four million lives. The case fatality estimates published for the 1918 pandemic were used as a base estimate for modeling the impacts of influenza which is thought to the most similar to an future pandemic (Peiris et al. 2004).

- 1918 Pandemic average case fatality rate 2.5% for the United States (Glezen 1996)
- 1918 Pandemic case fatality rate ranges from 2.5% to 50% (Noymer & Garenne 2000).
- Annual average for normal influenza deaths in the U.S. is 36,000 (Thompson et al. 2003).

While the percentage of people who became ill and died of the 1918 flu was 2 percent to 5 percent in the United States and Europe, it was more than 70 percent in some isolated native groups (Taubenberger et al. 2000). In Alaska, some villages were virtually wiped out by suffering a 25% mortality rate (Crosby 1989). Estimates for the U.S. range from the 2% to 33% due to the higher susceptibility of some populations. Case fatality rate estimates have ranged from 2.5% for the entire world to 5-70% for selected populations for the 1918 pandemic.

- Currently, the H5N1 case fatality rate is 58% (Yuen and Wong 2005)

At this moment, it is exceptionally problematic to predict the mortality rate that the H5N1 virus will bring if it becomes pandemic. Not only can we not accurately predict the virulence of the pandemic virus, the population immune status in a pandemic situation differs from that seen during the interpandemic period. At the onset of the previous pandemics, younger adults were immunologically naive to the new strains, whereas older populations may have been primed by previous infections of related strains that circulated in earlier times (Reid et al. 2001). Total global immune susceptibility to the avian influenza subtype H5N1 would be expected (Stephenson et al. 2004).

For this scenario we used both the lower estimate of case fatality of 2%.

Unlike the 1958 and 1968 pandemics, most deaths in the 1918 pandemic occurred among young adults, a group that usually has a very low death rate from influenza. Influenza and pneumonia death rates for 15 to 34 year olds were more than 20 times higher in 1918 than in previous years, with 99% of excess deaths among people under 65 years of age

(Taubenberger et al. 2000). Similar to the 1918 pandemic, Simonsen et al. (1998)
suggests that in the next pandemic might initially occur among persons < 65 years of age.